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Assessment of bronchodilator reponse by means of reactance parameters measured by the forced oscillation technique in subjects with chronic obstructive pulmonary disease (COPD)

Verbois, Camille

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ASSESSMENT OF THE BRONCHODILATOR RESPONSE BY MEANS OF REACTANCE PARAMETERS MEASURED BY THE FORCED OSCILLATION TECHNIQUE IN SUBJECTS WITH CHRONIC OBSTRUCTIVE PULMONARY DISEASE (COPD)

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Camille VERBOIS

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Université de Namur
FACULTE DE MEDECINE
Secrétariat des départements
Rue de Bruxelles 61 - 5000 NAMUR
Téléphone: + 32(0)81.72.43.22
E-mail: manon.chatillon@unamur.be - http://www.unamur.be/

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VERBOIS Camille, MARCHAND Eric
URPhyM, NARILIS, UNamur

Abstract

Background: COPD is a common chronic respiratory disease induced by smoking or exposition to noxious gases. The most disabling symptom is dyspnea and the first-line treatment to improve symptoms are bronchodilators. Usually, bronchodilator response is determined by the improvement of forced expiratory volume in one second (FEV_1) which is not well correlated to dyspnea. As the forced oscillation technique (FOT) allow to measure parameters related to lung hyperinflation, hallmark of severe COPD, which are better correlated with dyspnea, we reasoned that FOT might be an interesting tool to assess the bronchodilator response in COPD.

Aims: To:

- assess bronchodilator response both with conventional respiratory function tests and FOT, with a particular interest for reactance parameters which have been linked to lung hyperinflation.
- assess the correlation between respiratory parameters and intensity of dyspnea
- determine if changes in reactance parameters after bronchodilator administration are more closely related to those of IC than those of FEV_1.
- determine which changes in respiratory function parameters could predict a clinically significant improvement in IC.

Methods: 26 COPD patients were recruited. They were tested for conventional tests as well as with FOT both before and after bronchodilator administration (80 µg of ipratropium bromide and 200 µg of fenoterol hydrobromide).

Analysis: A majority of the parameters responded significantly after bronchodilator administration. A reactance parameter came out to be very interesting; the area above the reactance-frequency curve at 5Hz (AX5) which improved highly significantly after bronchodilator administration (p-value<0,001). More importantly, AX5 was correlated with dyspnea ($r = 0,41$, p-value<0,05) and the changes in AX5 were better correlated with the changes in IC ($r = -0,58$, p-value<0,01) than the changes in FEV_1 ($r = -0,47$, p-value<0,05). Finally, AX5 was shown to be a good predictor for a clinical and significant change in IC, as determined by ROC analysis (AUC=0,80, p-value<0,01).

Conclusion: AX5 parameter appears to be an interesting index for the assessment of the bronchodilator response. FOT also gives additional information to that of conventional respiratory function tests. Accordingly, and because of its ease of use, FOT appears to be an interesting method to assess bronchodilator response.

Keywords: Chronic Obstructive Pulmonary Disease, Forced Oscillation Technique, Bronchodilator Response, Reactance, Inspiratory Capacity

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Lastly, I thank the people who will take the time to read this manuscript.

"Success is the ability to go from failure to failure without losing your enthusiasm"
-Winston Churchill

"When everything seems to be going against you, remember that the airplane takes off against the wind, not with it"
-Henry Ford

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List of abbreviations

Abbreviation	Description
ATS	American thoracic society
AUC	Area under the curve
AX5	Area above the reactance-frequency curve at 5Hz
BD	Bronchodilator
BPM	Breaths per minute
CAT	COPD assessment test
Cm	Centimeter
cmH_2O	Centimeter of water
CO	Carbon monoxide
COPD	Chronic Obstructive Pulmonary Disease
DH	Dynamic pulmonary hyperinflation
DLCO	CO transfer capacity
EELV	End-expiratory lung volume
EFL	Expiratory flow limitation
ERV	Expiratory reserve volume
EVC	Expiratory vital capacity
FEV_1	Forced expiratory volume in one second
FEV_1/FVC ratio	Tiffeneau index
FOT	Forced oscillation technique
FRC	Functional residual capacity
Fres	Resonance frequency of the respiratory system
FVC	Forced vital capacity
GOLD	Global initiative for chronic obstructive lung disease
IC	Inspiratory capacity
KCO	CO transfer coefficient

Kg	Kilogram
L	Liter
m	Meter
Min	Minute
ml	milliliter
mmHg	Millimeter of mercury
MRC	Medical research council
n	Number of participants
N/A	Not applicable
NS	Not significant
PEEP	Positive end-expiratory alveolar pressure
R	Resistance
R_5	Resistance of the respiratory system at 5Hz
R5,in	Inspiratory resistance at 5Hz
R5,ex	Expiratory resistance at 5Hz
R_{19}	Resistance of the respiratory system at 19Hz
R_{19},in	Inspiratory resistance at 19Hz
R_{19},ex	Expiratory resistance at 19Hz
$R_{5–19}$	Difference between resistance of the respiratory system at 5 and 19Hz
$R_{5–19}$,in	Difference in inspiratory resistance between 5 and 19Hz
$R_{5–19}$,ex	Difference in expiratory resistance between 5 and 19Hz
RAW	Airway resistance
ROC	Receiver operating characteristic
RR	Respiratory rate
RV	Residual volume
s	Second
SD	Standard Deviation
sRAW	Specific airway resistance

SOBQ	Shortness of Breath Questionnaire
TGV	Thoracic gas volume
TLC	Total lung capacity
Va	Alveolar pressure
VC	Vital capacity
V_E	Minute ventilation
V_T	Tidal volume
WHO	World health organization
X	Reactance
X_5	Reactance of the respiratory system at 5Hz
X5,in	Inspiratory reactance of the respiratory system at 5Hz
X5,ex	Expiratory reactance of the respiratory system at 5Hz
ΔX5	Difference between inspiratory and expiratory reactance of the respiratory system at 5Hz
ΔIC	change in inspiratory capacity
ΔFEV_1	Change in forced expiratory volume in one second

1. Introduction

1.1. Chronic obstructive pulmonary disease

Chronic obstructive pulmonary disease (COPD) is a very common chronic respiratory disease which has a huge impact on the patients' quality of life. According to the World Health Organization (WHO), the prevalence of the disease was 251 million cases of COPD in the world in 2016 and more than 3.17 million people died of COPD in 2015, accounting for 5% of all deaths worldwide that year. It is also predicted that COPD will become the third cause of death in the world by 2020 [1] [2].

This disease is due to the inhalation of noxious gases and particles, mostly from tobacco smoke or exposure to occupational hazards. It is an incompletely reversible disease characterized by progressive airway narrowing and loss of lung elastic recoil resulting in airflow obstruction especially if risk factors persist, though the disease requires a certain level-duration of exposition to develop [3]. In these patients, airway inflammation causes wall thickening by hypertrophy of the smooth muscle, as well as reactive hypersecretion of mucus which induce a decrease of the diameter of the airway lumen and thus an increased airway resistance (see Figure 1) [4]. According to the Poiseuille equation ($R=8.\eta.L/\pi.r^4$)[1], when the radius decreases by half, resistance increases by 16 times [5].

COPD associated airway obstruction has a reversible part which is related to the contraction of airway smooth muscles that could be improved by the use of bronchodilators, inflammation and accumulation of mucus in the airway lumen. The irreversible part of airway obstruction is due to remodelling, especially fibrosis and narrowing of the diameter of peripheral airways as well as to the decrease in lung elastic recoil associated with emphysema (see below).

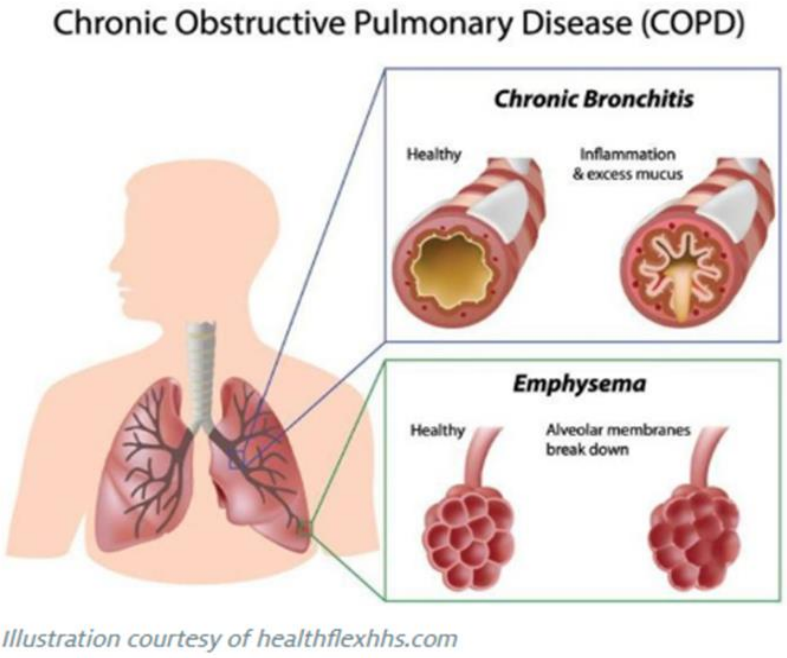

Figure 1. Illustration of the airway narrowing in COPD patient. Source: https://s3-ap-southeast-2.amazonaws.com/assets.asthmafoundation.org.nz/images/_fit640/COPD-diagram_160331_100539.jpg

[1] R = Resistance, η = gas viscosity, L = length of the tube, r = radius of the tube

The pathological abnormalities characterizing COPD are on the one hand a disease of the airways as discussed above and on the other hand, emphysema. The contribution of these two abnormalities varies from patient to patient. Worth of note, emphysema is not always associated with airflow obstruction. According to the GOLD guidelines, a patient with chronic bronchitis or emphysema cannot be considered as having COPD without the demonstration of airflow obstruction at pulmonary function tests [6].

1.1.1. Chronic bronchitis

Chronic bronchitis is defined on a clinical basis. It is defined by the presence of cough and sputum for at least three months per year during two consecutive years [7] [8]. It is associated with an excess of phlegm in the airways due to the hypertrophy of the submucous glands and the increased number of goblet cells responsible for cough and sputum. There is also an inflammatory infiltrate, a hypertrophy of smooth muscle and an increase in connective tissue. All these phenomena induce a reduction of the airway diameter and therefore induces bronchial obstruction. And finally have an impact on the resistance properties. It is important to notice that chronic bronchitis is not always present in COPD patients. Particularly, cough and sputum often disappear after smoking cessation.

1.1.2. Emphysema

On the other side, emphysema is defined on a pathological basis. It encompasses a destruction of the pulmonary alveoli wall with enlargement of the alveolar spaces. This reduces the surface for gas exchange and therefore the capacity of oxygen transfer towards the bloodstream [9]. Emphysema is responsible of a decrease in the pulmonary elastic recoil pressure at a given lung volume due to an increase in lung compliance. Rupture of the interalveolar septa is associated

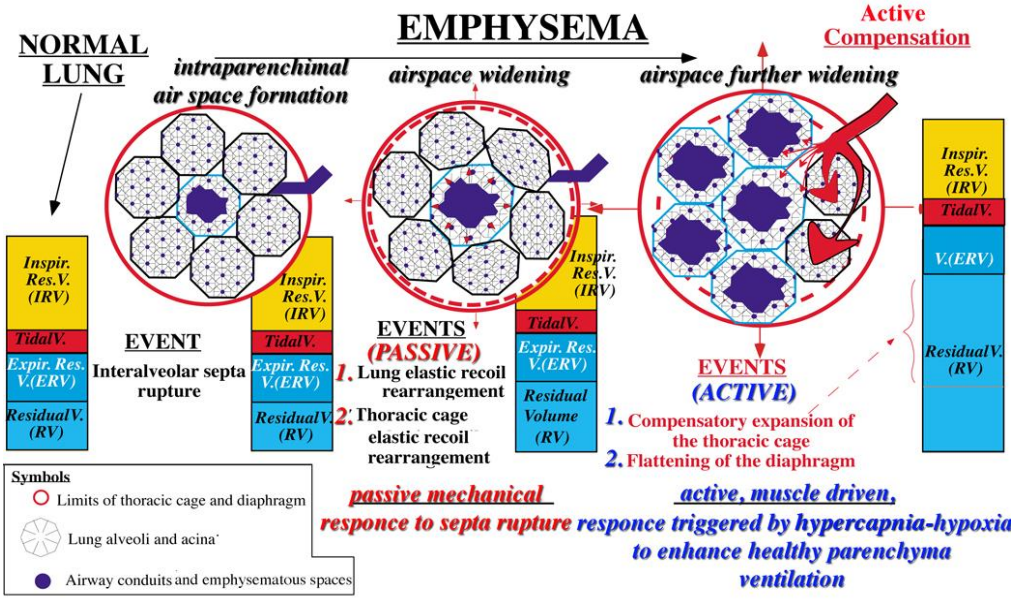

Figure 2. Illustration of the evolution of changes in lung volumes in case of emphysema. Source : http://www.fondazionecarrel.org/carrel/thorac/files/enphys/new/FIG_3_b.jpg

with a widening of the airspaces. This results in an increase in total lung capacity (TLC) and in particular in residual volume (RV) thus also an increase in functional residual capacity (FRC) (See Figure 2) [10]. This increased lung volume is called the lung hyperinflation and this is a major determinant of dyspnea in COPD since it is associated with a flattening of the diaphragm which puts the latter at mechanical disadvantage.

The decrease in lung elastic recoil is also an important mechanism for the increase in airway resistance. Indeed, the recoil of the lung provides a tethering effect on the airways which tends to increase their diameter. Thus, when there is a decrease of this lung elastic recoil, there is a reduction of the diameter of the small airways which has also an impact on the reduction in expiratory flows [11].

1.2. Dyspnea

The most disabling symptom of COPD is dyspnea, first induced by physical exercise but progressively worsening with disease progression such that it can even be present at rest. By definition, dyspnea is the feeling of not getting enough air to breath, also described as "air hunger" [12] [13]. But it is a subjective sensation felt by the patient, so the American Thoracic Society (ATS) decided to propose a broader definition of dyspnea for physicians, nurses and therapists which is "a term used to characterize a subjective experience of breathing discomfort that consists of qualitatively distinct sensations that vary in intensity" [14]. The modified Medical Research Council (mMRC) proposed a questionnaire which assesses the impact of dyspnea, it is the mMRC dyspnea scale that will be used in this study as well as the San Diego Shortness of Breath Questionnaire (French version) [15].

Dyspnea felt by the patient is related to the imbalance between inspiratory muscles capacity and the workload these muscles face. To be more precise, it is inversely related to the inspiratory muscle capacity and directly related to the requested inspiratory workload. COPD has an impact on these two factors as discussed below.

The end expiratory lung volume increases and as a consequence, the inspiratory capacity decreases due to different causes. First of all, the increased compliance of the lung (which is the inverse of the elastance), due to emphysema, leads to a resetting of the relaxation volume of the respiratory system to a higher level than in health, it is the static component of lung hyperinflation.

When airflow obstruction worsens, maximal expiratory flow may be achieved during tidal breathing, expiratory flow limitation (EFL) which is a pathophysiologic hallmark of COPD appears. This means that even with an increase in pressure drive, there is no increase in flow when EFL is present. In others words, there is no more expiratory flow reserve.

In patients with EFL during tidal breathing, the end-expiratory lung volume (EELV) is also dynamically determined and maintained at a level above the relaxation volume of the respiratory system. In flow-limited patients, the time-constant for lung emptying is increased in

many alveolar units but the expiratory time is often insufficient to allow EELV to reach to its normal relaxation volume, all this inducing air retention (or air trapping) called lung dynamic hyperinflation [12]. To summarize, EFL promotes dynamic pulmonary hyperinflation (DH) (See figure 3).

EFL has also an impact on the alveolar pressure. Indeed, as EELV is superior than the resting volume of the respiratory system when there is DH, the air surplus that stays in the lungs after the expiration creates a positive end-expiratory alveolar pressure (PEEP) (See figure 6) which needs to be neutralised by the inspiratory muscles before generating a negative alveolar pressure which is determinant to allow the inspiration. So, PEEP increases the inspiratory muscle workload.

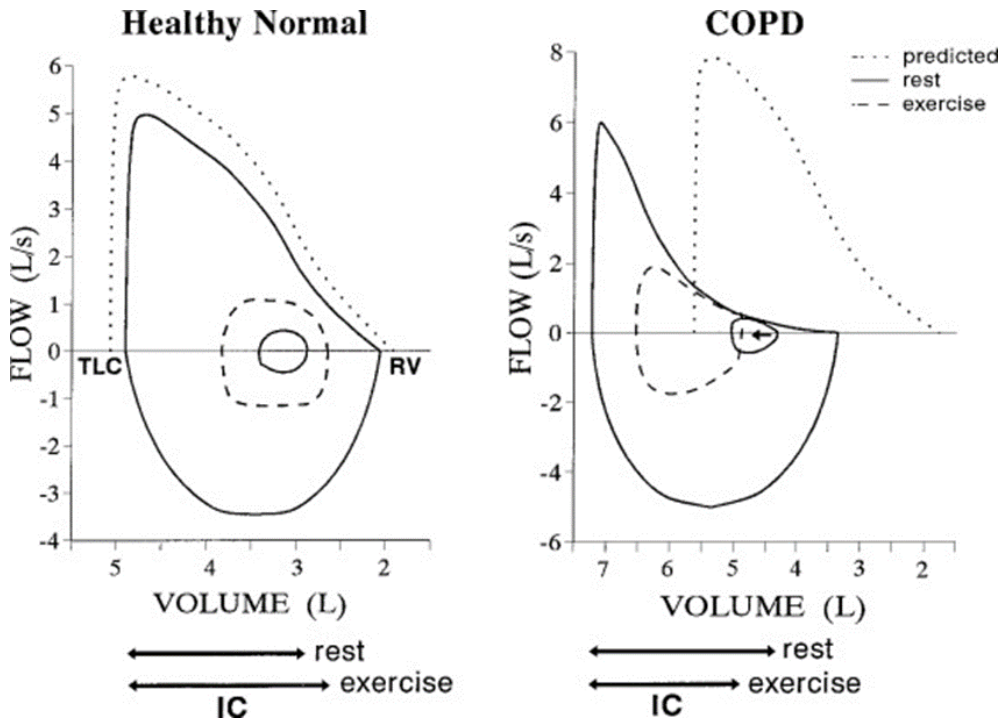

Figure 3. Illustration representing the flow-volume curves of an healthy subject (left panel) and a COPD patient (right panel). Continuous central lines represent the tidal breathing at rest and dotted central lines represent the tidal breathing during exercise. In COPD patient, there is a shift on the left to breathe during exercise inducing the patient to breathe at higher volume but also a decrease in the inspiratory capacity. Source : https://ars.els-cdn.com/content/image/1-s2.0-S0012369215527566-gr1.jpg

An important factor which decreases the inspiratory muscle capacity is the flattening of the diaphragm, the main inspiratory muscle. Indeed, due to lung hyperinflation, COPD patients have a flattened diaphragm which loses its dome shape. The vertical portion of the latter, also called the zone of apposition is shortened. This portion being the basis for its inspiratory effect, the decrease of its effectiveness due to DH is a real disadvantage because the inspiratory effort must be higher to inflate the lungs compared to healthy people (See Figure 4) [2]. This has a major contribution to the genesis of dyspnea in COPD [12 16].

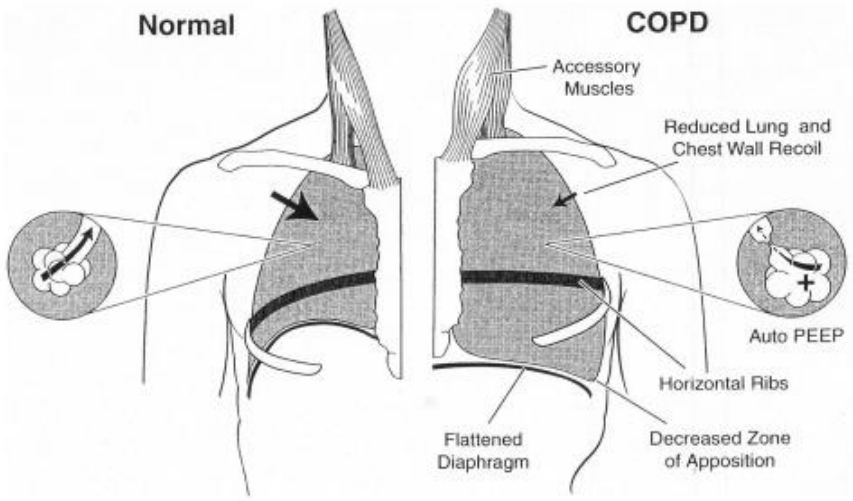

Figure 4. Illustration of the diaphragm flattening in COPD. Source : https://encrypted-tbn0.gstatic.com/images?q=tbn:ANd9GcSX7Wb7UMHwRCCVs_bsTTCZ1xvd_61i3nTdk9PIUy4ZGsxR3ts-rQ

The rate and magnitude of DH during exercise is generally measured in the laboratory setting by serial inspiratory capacity (IC) measurements. Because TLC, which is the volume of gas present in the lungs after maximal inspiration, is constant on the short term, a decrease in IC, which is the volume of air that can be inspired from EELV up to TLC, is due an increase in EELV, also called FRC. See Figure 5.

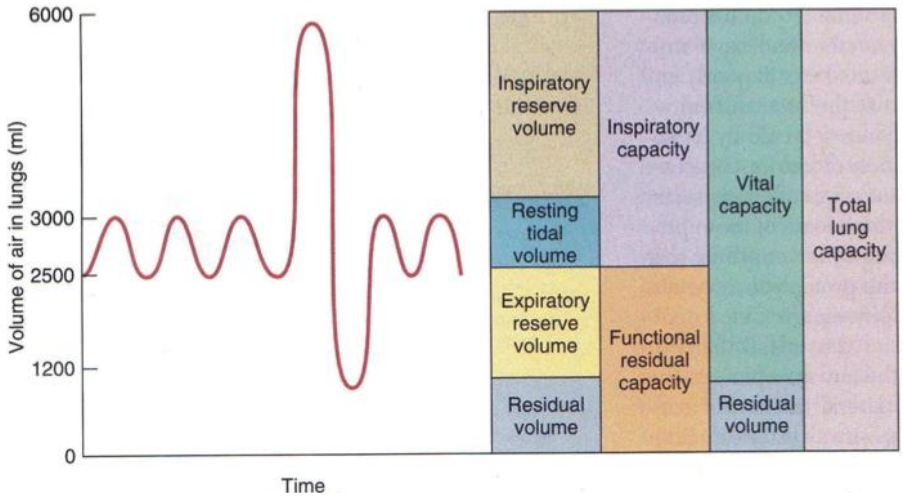

Figure 5. Illustration of lung volumes and capacitie. Source : https://upload.medbullets.com/topic/117009/images/screen%20shot%202012-02-17%20at%208.56.23%20pm.jpg

Regarding the inspiratory muscle workload, it has a resistive and an elastic component. The resistive one is proportional to the airway resistance (Raw) and the elastic component is proportional to the elastance properties. Due to different factors cited above, the airway resistance is increased inducing an increase of the resistive component of the inspiratory

muscles' workload. The elastic one also increases due to the fact that severe patients breathe at higher volume. It is represented on the right image on Figure 6, when a patient breath at higher volume, he breath on a flatter portion of the pressure-volume curve where the elastance is increase so there is an increase in the elastic component of the inspiratory muscles' workload. Accordingly, the dynamic compliance (measured during tidal breathing) is decreased due to DH as opposed to the static lung compliance which is increased due to emphysema.

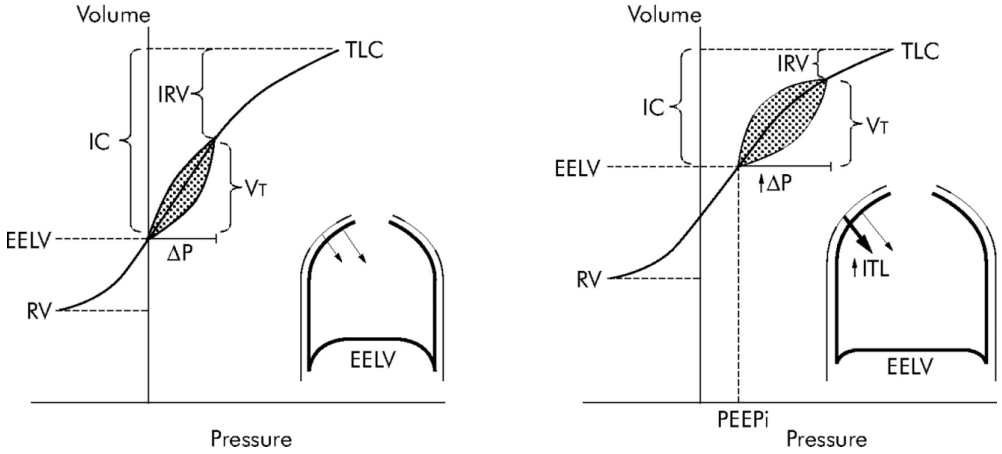

Figure 6. Illustration representing the pressure-volume curves of healthy subject (left) and COPD patient (right). Source : https://thorax.bmj.com/content/thoraxjnl/61/4/354/F3.large.jpg

1.3. Evaluation of the respiratory function

1.3.1. Forced vital capacity manoeuvre

There are different ways to evaluate the respiratory function but the most widely used is spirometry, especially the forced vital capacity manoeuvre (See Figure 7). This technique provides the following parameters:

- The forced expiratory volume in one second (FEV_1) which is usually used to assess COPD severity as a more pronounced decline is a sign of severity of the disease
- The forced vital capacity (FVC)
- With the above parameters, a third one can be calculated; the Tiffeneau index which is the FEV_1/FVC ratio. A reduction of this ratio to 70% or less after the administration of a bronchodilator is used to define the presence of airflow obstruction, which is included in the definition of COPD according to the GOLD guidelines [6 17].

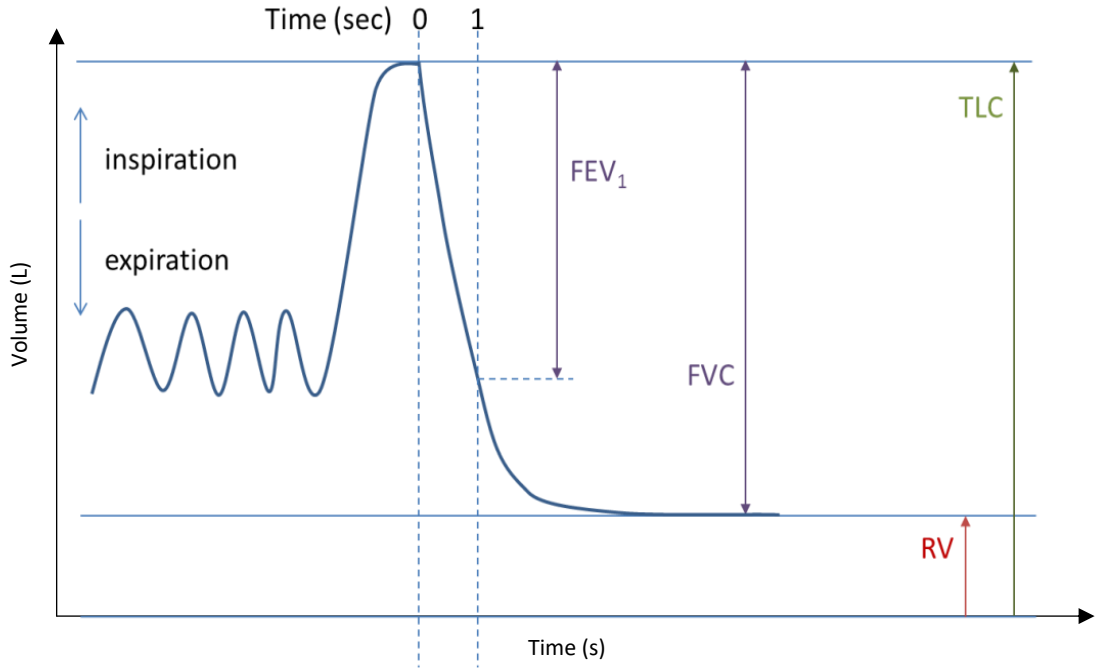

Figure 7. Tracing of FVC manoeuvre. Abbreviations: FEV_1: forced expiratory volume in one second ; FVC: forced vital capacity ; TLC: total lung capacity ; RV: residual volume. Source: http://bronchiectasis.com.au/wp-content/uploads/2015/09/Spirometry.png

1.3.2. Body plethysmography

Another test used to assess the respiratory function is the body plethysmography. It is a method where the patient is sitting in a closed cabin. Compared to spirometry, body plethysmography can measure the static lung volumes like residual volume (RV), functional residual capacity (FRC), total lung capacity (TLC) and airway resistance (RAW). This technique gives additional information regarding lung hyperinflation and airway resistance which are consequences of COPD. It has interest because it can give insight in the cause and the severity of dyspnea. Indeed, lung hyperinflation is associated with an increased FRC while airway resistance is directly related to the resistive work of breathing. As spirometry, body plethysmography requires a good collaboration from the patient which may be a limiting factor in their use in the case of for example, elderly people. Another issue of these two techniques is that they do not assess the reactance of the respiratory system. These disadvantages can be solved using another test called the FOT.

1.3.3. Forced oscillation technique

FOT is a method for non-invasively assessing respiratory mechanics during spontaneous breathing (tidal breathing). The FOT is based on the application of a sinusoidal pressure wave of specific frequency (from 5 to 37 Hz) within the airways, at the mouth of the patient [18] (See figure 8). It measures the impedance of the respiratory system and its two components:

- the respiratory system resistance which is mainly determined by the airway calibre and
- the respiratory system reactance which reflects its elastic and inertive [19] [20].

At low frequencies (typically 5Hz), the inertive component of the reactance is negligible and reactance mainly reflects the elastic properties of the respiratory system. Because the ability of the lungs to store energy is primarily manifest in the small airways, the reactance at 5Hz (X5) can provide information about the small airways. States such as hyperinflation result in more negative X5 values [21]. The more the lungs are hyperinflated, the more X5 values are negative.

Recently, it has been shown that the comparative analysis of low frequency reactance measured during the inspiratory and expiratory phases of the breathing cycle (ΔX5) makes it possible to detect the presence of EFL during tidal breathing which is an important determinant of DH and dyspnea in case of COPD, as discussed above. Indeed, Dellacà et al determined that a ΔX5 > 2,8, is an ideal criterion for detecting tidal EFL [22].

EFL is associated with what is called a choke point in the airways such that the oscillating pressure wave generated by the FOT system cannot travel downstream to a chokepoint. This results in a considerable decrease in the apparent compliance of the respiratory system. As flow limitation usually only occur during expiration, the reactance measured at low frequency during expiration is much more impaired than that measured in inspiration when EFL is present during tidal breathing. Accordingly, reactance parameters measured by FOT may capture physiological changes that are important for the pathogenesis of dyspnea which are not necessarily reflected by spirometry parameters or resistance parameters that can also be measured by FOT, and thus provide additional information [3].

Moreover, FOT can give information about the resistance of small airways [21]. Indeed, resistance measured at 5Hz represents total airway resistance and resistance measured at 19Hz represents the resistance of the upper airways. By subtracting R19 from R5 (R5-19), FOT gives information about small airways contrary to conventional respiratory function tests which give information only total airway resistance that is normally mostly influenced by the upper airways [21 23].

In addition to additional informations that it can provide regarding the physiology of the respiratory system, the FOT has another big advantage as compared to conventional pulmonary function tests: it is easy to use and does not require any particular maneuver to be performed by the patient. FOT measurements are indeed acquired during tidal breathing, requiring minimal cooperation of the patient [24].

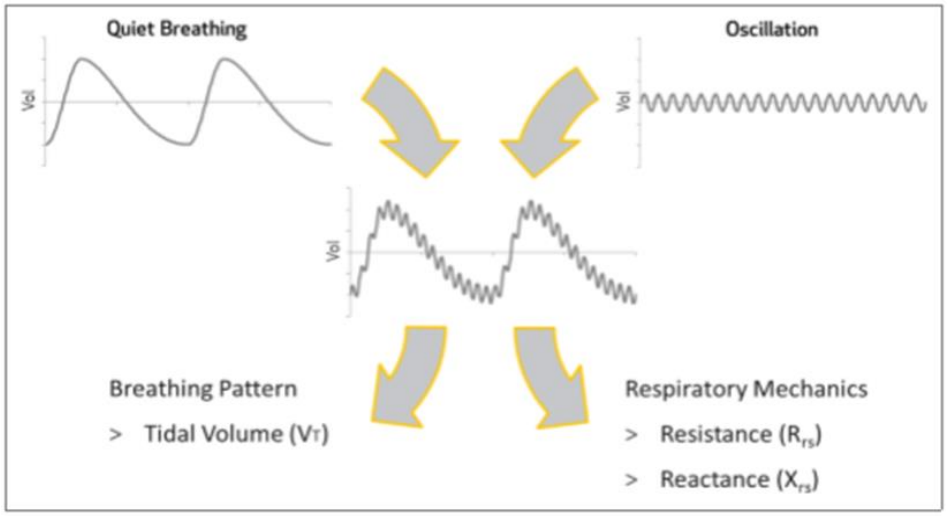

Figure 8. Illustration of the superposition of external pressure oscillations sent by the Tremoflo® to tidal breathing. Source : tremoFlo C-100 Airwave Oscillometry System User Manual

1.4. Bronchodilator response

Bronchodilators are used as first-line therapy in COPD with the aim to reduce symptoms, particularly improving dyspnea and exercise tolerance. They produce a rapid relaxation of airway smooth muscle and thus improve airway calibre and the expiratory flow rate. They lead to variable increases in FEV_1.

The response to bronchodilators can be assessed in a pulmonary functional test laboratory. The bronchodilator response is usually measured by the improvement of the FEV_1 (forced expiratory volume in one second). However, the correlation between symptoms especially dyspnea and FEV_1 is poor [25] [26]. Indeed, it has been shown that FEV_1 is a suboptimal index for assessing bronchodilator response. The performance of spirometry test is affected by the day of testing, the severity of baseline lung-function impairment and the number of drugs given to test [17].

Studies have examined the mechanisms of dyspnea relief after bronchodilatation, showing that bronchodilators reduce airway smooth muscle tone, improve airway conductance and enhance lung emptying. It accelerates the time constant for lung emptying in alveolar units throughout the lungs, thus reducing the dynamically determined end-expiratory lung volume (EELV) in patient with expiratory flow limitation. A reduced EELV (resulting in an increased IC) means reduced elastic load on and improved functional strength of the inspiratory muscles. All of these factors improve dyspnea [12]. Studies have shown there is a better correlation between dyspnea and inspiratory capacity (IC) than with FEV_1 [26]. Dyspnea increases with disease severity as the latter is associated with greater DH, and accordingly lower IC.

Regarding FOT, studies have shown that bronchodilator administration results in decreased resistance, especially in the small airways [27]. But they also showed that reactance parameters were good indicators for a reduction in EFL which is a critical determinant of dyspnea [27].

Accordingly, we reasoned that it would be useful to use the FOT to assess the changes in reactance after bronchodilator administration and their association with the changes in IC and FEV_1. We also were interested in the association between reactance indices and dyspnea experienced by the patients in their daily life.

2. Specific Aims

The objectives of the study were first to assess the bronchodilator response of parameters measured both by conventional spirometric and by FOT, in particular for the reactance parameters as they are related to EFL. These have been relatively forgotten in the literature at the expense of resistance parameters studied with both FOT and plethysmography.

The second objective was to evaluate the correlation between conventional respiratory function parameters, FOT parameters and dyspnea intensity assessed using the mMRC and San Diego SOBQ questionnaires.

Given that the correlation between dyspnea and FEV_1 is poor, it is therefore useful in a bronchodilator test to study the improvement of IC in addition to that of FEV_1 [25] [26]. Thus, the second objective was to assess if the improvement of the reactance parameter after bronchodilator administration is more closely related to that of IC than FEV_1.

The improvement of IC is not a routine for bronchodilator tests in most of the pulmonary functional labs. Moreover, as the forced vital capacity manoeuvre, its measurement requires a good patient collaboration. As the FOT is very simple to perform, because it does not need any cooperation of the patient, we were very interested in its use for the evaluation of reactance parameters and in particular, $\Delta X5$.

We were also particularly interested to assess whether changes in FOT parameters would predict significant changes in IC or FEV_1 after bronchodilatation [27].

3. Methods

3.1. Literature review

A majority of the articles were provided by Mr. Marchand. But the PubMed database was also consulted with keywords like “chronic obstructive pulmonary disease (COPD)”, “forced oscillation technique”, “reversibility test”, “bronchodilator” and “COPD management”.

3.2. Study sample and recruitment

Patients were recruited in the patient base of Mr. Marchand respecting the inclusion and exclusion criteria in the table below (See table 1). For a question of ease, the measurements were made the day of the consultation.

Inclusion criteria	Exclusion criteria
- Clinical diagnosis of COPD confirmed by post-bronchodilator (DUOVENT HFA 4 puffs) obstructive airway obstruction (FEV1/FVC < Percentile 5) persisting after bronchodilatation - Former or active smoking > 10 packs/year - Age > 40 years - Informed consent	- Inability to comply with bronchodilator weaning time: 6 hours for short-acting bronchodilators 12 hours for long-acting bronchodilators 24 hours for very long-acting bronchodilators - Inability to comply with the 4 hours of smoking cessation before the measurements - Inability to perform respiratory function tests - Continuous oxygen therapy - Close angle glaucoma - History of urinary retention (only for patients not usually treated with anticholinergic bronchodilators) - Pregnancy - Acute illness contraindicating the performance of respiratory tests

Table 1. Inclusion and exclusion criteria for the participation in this study.

3.3. Methodology/protocol

The ethical approval was obtained from the CHU UCL Namur site Godinne Ethics Committee on 5th March 2019. The trial was registered on clinicaltrial.gov on 9th April 2019 using the clinical trials identifier NCT03910985.

It was a monocentric study, all the measurements were done at the CHU UCL Namur, site Godinne.

A first contact with the patient was done by phone to explain the protocol of the study and answer their questions. Then the informed consent was sent to allow the patient to read it at home.

During the meeting before the tests, patients' questions were answered for a good understanding of the study. The informed consent was signed by the patient and the investigator (see Annex 1).

Then the followings items were obtained preceding the respiratory tests with a questionnaire (see Annex 2): anthropometric data (weight and size), personal data (date of birth, age, sex, smoking, number of cigarettes/day, pack/years, if former smoker : date of withdrawal and number of pack/years), medical data (medical background, thoracic surgical history, current medical treatment, the date of diagnosis of COPD and time of the last intake of inhaled treatments).

The assessment of symptoms, recommended by the Global Initiative for Chronic Obstructive Lung Disease (GOLD), was evaluated by using CAT questionnaire (CAT = COPD Assessment Test) and dyspnea by using mMRC scale (modified Medical Research Council) and the San Diego Shortness of Breath Questionnaire (French version). See Annex 3, 4 and 5.

The assessment of airflow limitation severity was evaluated by the level of FEV_1 after the administration of bronchodilator, to see the classification, see the table just below (Table 2) [6].

	Air flow limitation severity	FEV_1 predicted (%)
GOLD 1	Mild	$FEV_1 \geq 80$
GOLD 2	Moderate	$50 \leq FEV_1 < 80$
GOLD 3	Severe	$30 \leq FEV_1 < 50$
GOLD 4	Very severe	$FEV_1 < 30$

Table 2. Classification of airflow limitation severity in COPD (based on post-bronchodilator FEV_1 in patients with $FEV_1/FVC < 0.70$) according to GOLD guidelines.

Once the patient had answered the different questionnaires, he was weighed and measured. The functional respiratory measures were done in this order:

- FOT,
- total lung capacity (TLC),
- airway resistance (Raw),
- slow vital capacity (slow VC including IC measurement),
- forced vital capacity (FVC) manoeuvre with measurement of FEV_1 and FEV_1/FVC ratio and
- carbon monoxide (CO) diffusion indices.

Then a short-acting bronchodilator (DUOVENT HFA® 4 puffs) was administrated using an inhalation chamber. After 30 minutes of waiting, tests were carried out again in the same order except for diffusion indices.

a). Forced oscillation technique

The test started with the TREMOFLO (Thorasys Thoracic Medical System Inc., Montreal, Canada). It was necessary to do the FOT before the spirometry because the forced manoeuvres of spirometry have an impact on resistance and reactance values [21].

The patient was sit straight on a chair with uncrossed legs, hands on cheeks to avoid any bias due to cheeks compliance, in order to minimize the upper airway artefact [18]. Because pressure oscillations are applied at the mouth, there are oscillatory motion in the mouth cavity and the extrathoracic airways which affect the results of measurements which it is called the upper airway artefact. Indeed, if the cheeks are not held, R_{20} values reduce significantly and are therefore underestimated. It affects also the R_5 and X_5 significantly [18 21].

During the test, the patient wore a nose-clip and breathed through a mouthpiece. It was important to check that the patient putted the mouthpiece in the right way, that means that the mouthpiece should be entirely in the mouth and the patient's teeth should tighten the plastic end thereof. Once the device and the patient were ready, the test started. The patient breathed normally through the pneumotachograph (tidal breathing) and when breathing was stable, oscillations waves were sent during 20 seconds for a run. Minimum three runs were needed and maximum eight runs.

The parameters that were kept with this technique are the mean of all these measurements: the resistance of the respiratory system at 5 and 19 Hz ($R_{5...19}$) during the entire respiratory cycle, the difference in resistance between 5 and 19Hz (R_{5-19}), the inspiratory resistance at 5Hz (R_5,in), the expiratory resistance at 5Hz (R_5,ex), the inspiratory resistance at 19Hz (R_{19},in), the expiratory resistance at 19Hz (R_{19},ex), the difference in inspiratory resistance between 5 and 19Hz (R_{5-19},in), the difference in expiratory resistance between 5 and 19Hz (R_{5-19},ex), the reactance of the respiratory system at 5 Hz (X_5) during the entire respiratory cycle, the resonance frequency of the respiratory system at 5 Hz (f_{res}), area above the reactance-frequency curve at 5Hz up to FRes (AX_5), the difference between inspiratory and expiratory reactance at 5Hz (ΔX_5), the expiratory reactance at 5 Hz (X_5,ex), the inspiratory reactance at 5 Hz (X_5,in), respiratory rate (RR), the minute ventilation (V_E) and tidal volume (V_T).

To accept a run, it was necessary to have less than 15% coefficient of variation for R_5 and AX (See Figure 9).

Figure 9. Illustration of the Tremoflo results window which stands out in three panels. The left panel represents the navigation plane with the different runs of measurements made. The midst panel is the impedance chart with following graphical parameters measured at various oscillation frequencies represented on the x-axis: the top curve with squares represents the resistance (R) values and the bottom curve with circles represents the reactance (X) values. Thin curves with represent each individual measurements of the patient. Thick curves represent average values acquired in different runs for R and X at various frequencies. Continuous black curves represent the predicted values according to the patient age, sex, height and weight and dashed lines represent the higher limits of normal for R and lower limit of normal for X. On the right panel, test mean values recorded in the patient are expressed on a green-to-red Gauge scales to easily visualize the state of a patient's respiratory mechanics relative to their predicted values, the significance of the individual colours is as follows : green for measurements within the 95% confidence interval of normal, yellow for outcome close to the upper or lower limit of normal and red for outcome outside of the 95% confidence interval around normal value. The yellowed area represents the area above the reactance-frequency curve at 5Hz. Source: tremoFlo C-100 Airwave Oscillometry System User Manual

b). Total lung capacity and thoracic gas volume

For this test, the patient was sitting with uncrossed legs in a plethysmograph, wearing a nose-clip and a mouthpiece supporting his cheeks in both hands to avoid upper airway bias, see previous paragraph for the explanations. The cabin door was closed and a waiting time of 1 minute was required to allow the thermic stabilisation of the cabin.

The patient breathed normally and when tidal breathing was stable, the shutter was closed at the end of an expiration. The duration of the occlusion lasting approximately 3 seconds and the patient continued to breathe during this one. When the shutter was reopened, the patient inspired deeply followed by a long and complete exhalation to the residual volume (RV) which is the volume of gas remaining in the lungs after forced expiration. The manoeuvre was ended by a maximal inspiration (to see the manoeuvre of this technique see Figure 10, Panel B). This manoeuvre allowed us to measure

- the thoracic gas volume (TGV) which is the volume of intrathoracic gas measured by plethysmography at the time of closing of the shutter, corresponding to FRC. The TGV is the volume compressible gas present inside the thorax at the closing of the shutter;
- the residual volume (RV) which is the TGV diminished by the expiratory reserve volume (ERV; Figure 10);
- the total lung capacity (TLC) which is the volume of gas present in the lungs after maximal inspiration which is also the sum RV and vital capacity (VC) [28].

Three to five technically satisfactory maneuvers were obtained with a maximal 5% variability between the 2 best measurements for TLC and TGV and maximal 5% and 150 mL variability for VC [29]. The highest reproducible value was kept for analysis.

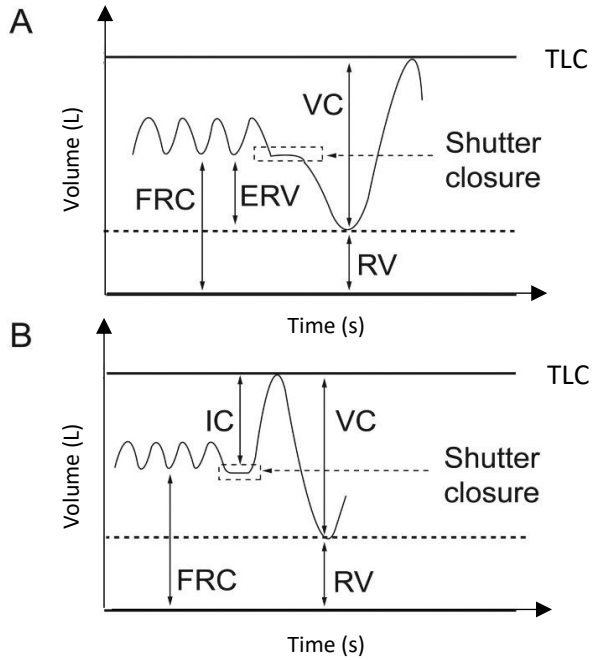

Figure 10. Tracing of TLC manoeuvre. Abbreviations: TLC: total lung capacity ; VC: vital capacity ; FRC: functional residual capacity ; RV: residual volume ; ERV: expiratory reserve volume ; IC: inspiratory capacity. Source: http://rc.rcjournal.com/content/respcare/57/7/1076/F1.large.jpg

c). Airway resistance

For this test, the patient was sitting upright in the plethysmograph, to avoid the compression of airways, wearing a nose-clip and a mouthpiece supporting his cheeks in both hands to avoid bias and uncrossed legs. The cabin door was closed and a waiting time of 1 minute was required to allow the thermic stabilisation of the cabin.

The patient breathed rhythmically following the operator (panting manoeuvre) while captures were taken with the device. Then the shutter was closed at the end of an expiration. It was necessary to continue breathe during this one. When the shutter was reopened, the test stopped.

This manoeuvre allowed us to have airway resistance (RAW) which comprises the resistance produced by the chest wall, lung tissue and the airway, and specific airway resistance (sRAW) which is the product of the airway resistance and FRC.

First, sRAW was evaluated through simultaneous recording of airflow and plethysmographic volume swing during tidal breathing. TGV was evaluated through recording of plethysmographic volume swing and the corresponding mouth pressure swing while the patient performed panting manoeuvre against a closed shutter. Then RAW was calculated as the ratio of sRAW/TGV [30].

It was important to notice that due to the panting manoeuvre, TGV that was measured with this technique might be higher than the TGV of the previous technique. It is due to the fact that when a rhythm is imposed to the patient, he compensates and thus increases his TGV.

Three to five technically satisfactory tests were have to be obtained with less than 5% of variation between the two best measurements [29] [30]. The highest reproducible of each value is the one that we kept.

d). Inspiratory capacity

It is preferable that slow IC (inspiratory capacity) and VC (vital capacity) manoeuvres were performed before FVC (forced vital capacity) manoeuvres to minimize the risk of

- modification of small airway smooth muscle tone;
- interference with patient fatigue induced by forced manoeuvres.

For this test, the patient was tested in a sitting position wearing a nose-clip with no air leaks between the mouth and the mouthpiece. The patient started to breathe normally (tidal breathing) until quiet tidal breathing is stabilized, followed by an inspiratory manoeuvre to TLC to record IC, followed by a full expiration to RV to record the expiratory vital capacity (EVC) (see Figure 11). The manoeuvre was not forced but the patient had to understand that he had to completely inflate and thereafter empty his lungs [31]. This manoeuvre allowed us to have slow IC and VC which are respectively the maximum gas volume that can be inspired from the functional residual capacity (FRC) and the volume of gas mobilized at the mouth between full inspiration and complete expiration [28].

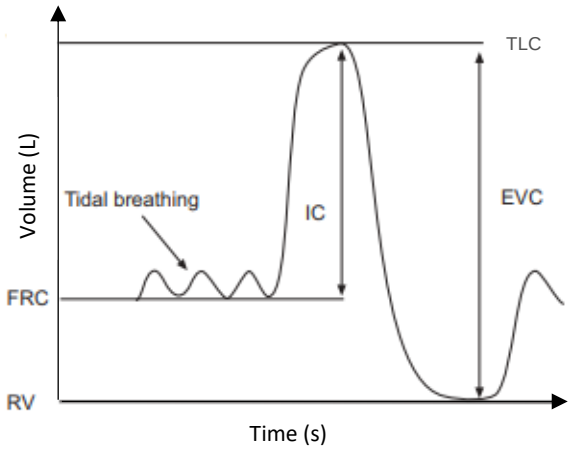

Figure 11. Tracing of IC manoeuvre. Abbreviations: TLC: total lung capacity ; FRC: functional residual capacity ; RV: residual volume ; IC: inspiratory capacity ; EVC: expiratory vital capacity. Source: https://www.thoracic.org/statements/resources/pfet/PFT2.pdf

Minimum three tests with acceptable values were needed and maximum eight tests were done. The variation of the measurements of slow IC and VC was not to be greater than 150 ml and 5% between the two best measurements. The highest reproducible of each value is the one that we kept.

e). Forced vital capacity

For this test, the patient was tested in a sitting position wearing a nose-clip with no air leaks between the mouth and the mouthpiece.

The manoeuvre was composed of three distinct phases, the patient first breathed normally (tidal breathing) then he inspired quickly and thoroughly from the functional residual capacity (FRC) follows by a ‘‘blast’’ of exhalation to the residual volume (RV) of minimum 6 seconds, to empty his lungs to the maximum. Then the patient ended with a deep inspiration (see Figure 7). This manoeuvre allowed us to have forced vital capacity (FVC) which is the maximum volume of air exhaled during a maximal effort performed from a maximum inspiration and the forced expiratory volume in one second (FEV_1) which is the maximum volume of air exhaled during the first second of a forced expiration from a maximum inspiration [28] [31].

Minimum three tests with acceptable values were needed and maximum eight tests were done. The difference for the FVC and FEV_1 was not to be greater than 150 ml between the two best measurements [31]. The highest reproducible of each value is the one that we kept.

f). Diffusion indices

This test was used to measure the diffusion of carbon monoxide with the use of a gas test composed of carbon monoxide (CO) and a tracer gas (helium) to measure the alveolar volume (V_A). The tracer gas should be relatively insoluble as well as chemically and biologically inert. Given that the tracer gas was used to determine the initial alveolar concentration of CO, as well as the alveolar volume from which CO diffuses, its diffusion should therefore be similar to that of CO. It should not influence the measurement of CO concentration. It was important that it does not exist naturally in the alveolar gas, that’s why helium was used as a tracer gas, because he fulfils the majority of these criteria.

Concerning the method, once the mouthpiece and the nose-clip were in place, the patient breathed normally through the pneumotachograph (tidal breathing) and when it was stable, the manoeuvre started with a non-forced exhalation to the residual volume (RV). In case of COPD, the expiration to the residual volume may take longer time, so it will be useful to limit the duration of this manoeuvre to six seconds. When the residual volume was reached, the gas test was released and the patient inspired quickly to the total lung capacity (TLC). Then an apnoea of ten seconds was requested; this action was required to allow CO to diffuse from the alveolar compartment to the blood compartment. When the time was up, the patient performed a rapidly exhaled air for approximately four seconds with a collection duration of three seconds. The sample taken during this expiration was used to evaluate helium and CO concentrations still

present in the lungs. The changes in concentrations allowed us to calculate diffusion indices ; the CO transfer coefficient (KCO), which is the capture of pulmonary CO measured as the fall in alveolar CO concentration, was multiplied by the volume of gas accessible to the CO (alveolar volume) to obtain DLCO which is the total capacity of CO transfer.

Two tests with a variation less than 3ml/min/mmHg were recommended with a waiting time of 4 minutes between the tests to allow adequate elimination of test gases from the lungs. Deep inspirations helped eliminate gas more effectively. It was recommended that the patient remains seated during this waiting time. Maximum five tests were done [32]. The highest reproducible of each value is the one that we kept.

g). Bronchodilator response

To study the bronchodilator response in this study, 4 puffs of DUOVENT HFA® (corresponding to 80 µg of ipratropium bromide and 200 µg of fenoterol hydrobromide) were administered using an inhalation chamber.

A waiting time of 30 minutes was required before starting the manoeuvre previously done, except for the diffusion which was performed only pre-bronchodilator.

3.4. Privacy and confidentiality

Patients' data were collected after the signature of the informed consent. The data are confidential and the anonymity is guaranteed. If the collected data have an interest in the patient's medical follow-up, the relevant data can be sent to the patient's physician except if the patient disagree.

3.5. Statistical analysis

Measurements before and after bronchodilators were compared by student t-test for paired samples or by Wilcoxon test if the conditions of normality were not be fulfilled. To assess the normality, shapiro-wilk test was used.

The following relationships were evaluated by linear regression and Pearson or Spearman correlation coefficient, as required:

Changes after bronchodilators in the parameters measured by forced oscillation on the one side and FEV_1 and IC on the other side,

IC and various respiratory function parameters measured after bronchodilators on the one side and dyspnea indices on the other side;

The predictive character of an improvement in IC (> 10% predicted value) or an improvement in FEV_1 (200 mL and 12%) were determined for the bronchodilator response of various functional parameters with the use of the ROC method.

The statistical threshold of significance was set at 0.05 (two-sided test).
All data were analysed using R-studio statistic program Version 1.1.456, with the exception of ROC curves which were generated using the NCSS 11 Statistical Software (version 11.0.12). NCSS, LLC. Kaysville, Utah, USA.

4. Results

4.1. Study population

The baseline characteristics of the 26 patients involved in this study are described in table 3. As shown in the table, there was a majority of men. GOLD stage 2 and 3 were equally represented but stage 1 and 4 were underrepresented. MRC stage 2 and 3 were equally represented but stage 0, 1 and 4 were underrepresented.

Table 3. Baseline characteristics of the patients.

Characteristics	Value (Mean ± SD)
n	26
Age (years)	65,7 ± 7,32
Gender (male/female)	21/5
Smokers/Ex-Smokers	7/19
Height (cm)	172 ± 9
Weight (kg)	70 ± 18
BMI (kg/m²)	23,7 ± 4,7
GOLD classification (1/2/3/4)	1/10/11/4
CAT score	19,5 ± 8,1
MRC Scale (0/1/2/3/4)	2/1/9/9/5
San Diego SOBQ	53,4 ± 29,8

All values are presented as absolute numbers or mean ± SD. Abbreviations: n: number of participants; SD: standard deviation; BMI: body mass index ; GOLD: Global initiative for chronic obstructive lung disease ; CAT: COPD assessment test ; mMRC: modified Medical Research Council ; SOBQ: shortness of breath questionnaire.

4.2. Bronchodilator response for the respiratory function tests

Table 4 describes the results of the respiratory function tests before and after the inhalation of the bronchodilator. The TGV, TLC and RV parameters were measured in 25 patients, while the others were measured in 26, because for one patient the plethysmograph cabin could not detect mouth pressure changes and therefore did not provide any data for these three parameters in that case.

All the conventional respiratory tests significantly improved following the administration of DUOVENT HFA® except for the Tiffeneau index (p-value > 0,05).

Table 4. Baseline respiratory function tests results of the patients.

Baseline characteristics	Pre-BD (Mean ± SD)	Post-BD (Mean ± SD)	p-value
FEV1 (L)	1,19 ± 0,61	1,38 ± 0,62	<0,001
FEV1 (% predicted)	41 ± 16	47 ± 17	<0,001
FVC (L)	2,94 ± 0,77	3,40 ± 0,79	<0,001
FVC (% predicted)	81 ± 18	93 ± 19	<0,001
Tiffeneau (%)	40 ± 13	40 ± 12	NS
Tiffeneau (% predicted)	52 ± 17	52 ± 17	NS
VC (L)	3,21 ± 0,83	3,52 ± 0,89	<0,001
VC (% predicted)	84 ± 16	93 ± 18	<0,001
IC (L)	2,16 ± 0,55	2,37 ± 0,58	<0,01
IC (% predicted)	79 ± 16	86 ± 17	<0,01
TGV (L) (n=25)	5,55 ± 1,38	5,00 ± 1,12	<0,001
TGV (% predicted)	164 ± 39	149 ± 34	<0,001
TLC (L) (n=25)	7,54 ± 1,35	7,22 ± 1,12	<0,01
TLC (% predicted)	119 ± 18	114 ± 17	<0,01
RV (L) (n=25)	4,83 ± 1,39	4,03 ± 1,18	<0,001
RV (% predicted)	204 ± 60	171 ± 54	<0,001
RAW (cmH2O/L/S)	4,74 ± 2,19	3,37 ± 2,16	<0,001

RAW (% predicted)	368 ± 172	262 ± 171	<0,001
sRAW (cmH2O*s)	31,5 ± 18,9	22,6 ± 18,1	<0,001
sRAW (% predicted)	726 ± 435	521 ± 416	<0,001
DLCO (mL/mmHg/min)	16,7 ± 8,6	N/A	N/A
DLCO (% predicted)	52 ± 22	N/A	N/A
KCO (DLCO/L)	2,79 ± 1,29	N/A	N/A
KCO (% predicted)	58 ± 27	N/A	N/A

All values are presented as mean ± SD. Abbreviations: SD: standard deviation ; BD: bronchodilator ; FEV1: forced expiratory volume in one second ; FVC: forced vital capacity ; VC: vital capacity ; IC: inspiratory capacity ; TGV: thoracic gas volume ; TLC: total lung capacity ; RV: residual volume ; RAW: airway resistance ; sRAW: specific airway resistance ; DLCO: CO transfer factor ; KCO: CO transfer coefficient ; N/A: not applicable ; NS: not significant.

4.3. Bronchodilator response for parameters measured by FOT

Table 5 describes the FOT parameters before and after bronchodilator administration. All FOT parameters significantly improved following bronchodilator administration, except for R19, R19ex, ΔX5 and RR (p-value > 0.05). In contrast, the change in AX5 was highly significant (p-value < 0,001).

Fres parameter was not included in the analysis because 14 COPD patients in pre-bronchodilator test and 8 in post-bronchodilator test had a Fres superior to the higher frequency analysed by the Tremoflo® inducing a not applicable result.

As said above, a ΔX5 > 2,8 was a surrogate for EFL detection. Nine patients had EFL according to this criterion in pre-bronchodilator condition and 9 in post-bronchodilator condition of whom 8 also had EFL pre-bronchodilator administration. Only one patient with EFL before bronchodilator became non EFL after the administration of bronchodilator. This patient had a good response for all the others parameters.

As opposed to expectations, one patient without EFL in pre-bronchodilator condition presented EFL after the administration of DUOVENT HFA®, despite that all other parameters responded after the administration of bronchodilator.

Table 5. Baseline and post-BD FOT parameters.

Baseline characteristics	Pre-BD (Mean ± SD)	Post-BD (Mean ± SD)	p-value
R5 ($cmH_2O.s/L$)	5,24 ± 1,62	4,71 ± 1,58	<0,001
R19 ($cmH_2O.s/L$)	2,99 ± 0,96	2,88 ± 1,03	NS
R5-19 ($cmH_2O.s/L$)	2,25 ± 0,81	1,83 ± 0,73	<0,001
R5,in ($cmH_2O.s/L$)	4,83 ± 1,46	4,04 ± 1,36	<0,001
R5,ex ($cmH_2O.s/L$)	5,51 ± 1,82	5,17 ± 1,82	<0,05
R19,in ($cmH_2O.s/L$)	3,14 ± 1,01	2,94 ± 1,06	<0,05
R19,ex ($cmH_2O.s/L$)	2,89 ± 0,95	2,84 ± 1,04	NS
R5-19,in ($cmH_2O.s/L$)	1,69 ± 0,66	1,10 ± 0,62	<0,001
R5-19,ex ($cmH_2O.s/L$)	2,62 ± 0,99	2,33 ± 0,90	<0,05
X5 ($cmH_2O.s/L$)	-4,88 ± 2,12	-4,09 ± 1,78	<0,01
AX5 (cmH_2O/L)	57,4 ± 28,3	44,6 ± 24,1	<0,001
ΔX5 ($cmH_2O.s/L$)	2,45 ± 2,45	2,15 ± 2,16	NS
X5,in ($cmH_2O.s/L$)	-3,40 ± 1,28	-2,73 ± 1,03	<0,001
X5,ex ($cmH_2O.s/L$)	-5,85 ± 2,94	-4,88 ± 2,44	<0,01

All values are presented as mean ± SD. Abbreviations: SD: standard deviation ; BD: bronchodilator ; R5: resistance at 5Hz ; R19: resistance at 19Hz ; R5-19: difference in resistance between 5 and 19Hz ; R5in: inspiratory resistance at 5Hz ; R5ex: expiratory resistance at 5Hz ; R19 in: inspiratory resistance at 19Hz ; R19ex: expiratory resistance at 19Hz ; R5-19in: difference in inspiratory resistance between 5 and 19Hz ; R5-19ex: difference in expiratory resistance between 5 and 19Hz ; X5: reactance at 5Hz ; AX5: area above the reactance-frequency curve at 5Hz ; ΔX5: difference between inspiratory and expiratory reactance at 5Hz ; X5ex: expiratory reactance at 5Hz ; X5in: inspiratory reactance at 5Hz ; V_T: tidal volume ; RR: respiratory rate ; V_E: minute ventilation ; NS: not significant.

4.4. Correlations between the modified Medical Research Council dyspnea questionnaire score and respiratory function parameters

There was no significant correlation between the different respiratory function parameters including those measured by FOT and the modified Medical Research Council questionnaire dyspnea score neither in pre-bronchodilator nor is post-bronchodilator condition. All p-values were superior to 0,05.

4.5. Correlations between the San Diego Shortness of Breath Questionnaire score and respiratory function parameters

Table 6 describes the correlation between the respiratory parameters and the intensity of dyspnea assessed by the San Diego SOBQ questionnaire after the inhalation of the bronchodilator. There was a significant correlation with IC, RAW, R5, R5-19, R5ex, X5 and AX5.

Table 6. Correlations between respiratory functions parameters and the intensity of dyspnea assessed by the San Diego SOBQ questionnaire.

	San Diego SOBQ questionnaire	
	r	**p-value**
Respiratory parameters		
FEV1 (L)	-0,30	NS
FVC (L)	-0,30	NS
VC (L)	-0,35	NS
IC (L)	-0,44	<0,05
TGV (L)	0,05	NS
TLC (L)	-0,18	NS
RV (L)	0,14	NS
DLCO*	-0,20	NS
KCO*	-0,10	NS
RAW (cmH2O/L/S)	0,47	<0,05
R5 ($cmH_2O.s/L$)	0,40	<0,05
R19 ($cmH_2O.s/L$)	0,26	NS
R5-19 ($cmH_2O.s/L$)	0,49	<0,05
R5,in ($cmH_2O.s/L$)	0,37	NS
R5,ex ($cmH_2O.s/L$)	0,40	<0,05
X5 ($cmH_2O.s/L$)	-0,40	<0,05
AX5 (cmH_2O/L)	0,41	<0,05

ΔX5 ($cmH_2O.s/L$)	0,30	NS
X5,in ($cmH_2O.s/L$)	-0,26	NS
X5,ex ($cmH_2O.s/L$)	-0,38	NS

*Abbreviations: BD: bronchodilator ; FEV1: forced expiratory volume in one second ; FVC: forced vital capacity ; VC: vital capacity ; IC: inspiratory capacity ; TGV: thoracic gas volume ; TLC: total lung capacity ; RV: residual volume ; RAW: airway resistance ; R5: resistance at 5Hz ; R5-19: difference in resistance between 5 and 19Hz ; R5in: inspiratory resistance at 5Hz ; R5ex: expiratory resistance at 5Hz ; X5: reactance at 5Hz ; AX5: area above the reactance-frequency curve at 5Hz ; ΔX5: difference between inspiratory and expiratory reactance at 5Hz ; X5ex: expiratory reactance at 5Hz ; X5in: inspiratory reactance at 5Hz ; NS: not significant ; r : correlation coefficient. *These parameters were only measured in pre-bronchodilator condition.*

Figure 12 shows the most interesting correlations for this study.

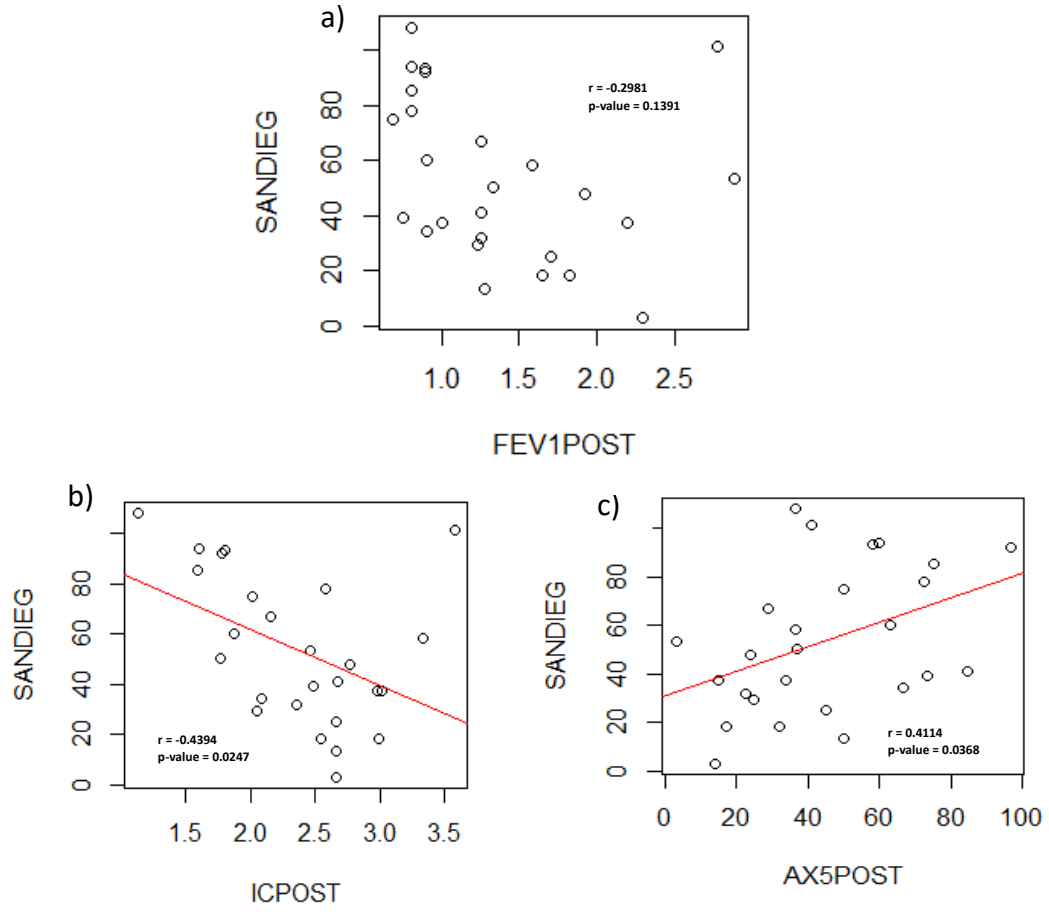

Figure 12. Correlations between respiratory functions parameters and intensity of dyspnea assessed by the San Diego SOBQ questionnaire score (SANDIEG) after the bronchodilator inhalation. Abbreviations: FEV1POST: Post-bronchodilator Forced Expiratory Volume in one second ; ICPOST: post-bronchodilator inspiratory capacity ; AX5POST: post-bronchodilator area above the reactance-frequency curve at 5Hz ; r : correlation coefficient.

4.6. Correlations between the changes of inspiratory capacity and the changes of other respiratory function parameters after bronchodilator administration

Table 7 describes the correlations between the variation of IC and the variation of the respiratory function parameters after bronchodilator administration. The change in VC, TGV, RV, R5, R5in, AX5 and X5in were significantly correlated with the change of IC.

Table 7. Correlations between the change in inspiratory capacity (ΔIC) and the change in respiratory function parameters (Δ respiratory parameters) after bronchodilator administration.

	Δ IC	
	r	**p-value**
Δ Respiratory parameters		
FEV_1 (L)	0,20	NS
FVC (L)	0,07	NS
VC (L)	0,45	<0,05
TGV (L)	-0,53	<0,01
TLC (L)	-0,21	NS
RV (L)	-0,65	<0,001
RAW (cmH2O/L/S)	-0,13	NS
R5 ($cmH_2O.s/L$)	-0,43	<0,05
R19 ($cmH_2O.s/L$)	-0,33	NS
R5-19 ($cmH_2O.s/L$)	-0,31	NS
R5,in ($cmH_2O.s/L$)	-0,59	<0,01
R5,ex ($cmH_2O.s/L$)	-0,23	NS
X5 ($cmH_2O.s/L$)	0,37	NS
AX5 (cmH_2O/L)	-0,58	<0,01
ΔX5 ($cmH_2O.s/L$)	-0,11	NS
X5,in ($cmH_2O.s/L$)	0,53	<0,01
X5,ex ($cmH_2O.s/L$)	0,28	NS

Abbreviations: BD: bronchodilator ; FEV1: forced expiratory volume in one second ; FVC: forced vital capacity ; VC: vital capacity ; IC: inspiratory capacity ; TGV: thoracic gas volume ; TLC: total lung capacity ; RV: residual volume ; RAW: airway resistance ; R5: resistance at 5Hz ; R19: resistance at 19Hz ; R5-19: difference in resistance between 5 and 19Hz ; R5in: inspiratory resistance at 5Hz ; R5ex: expiratory resistance at 5Hz ; X5: reactance at 5Hz ; AX5: area above the reactance-frequency curve at 5Hz ; ΔX5: difference between inspiratory and expiratory reactance at 5Hz ; X5ex: expiratory reactance at 5Hz ; X5in: inspiratory reactance at 5Hz ; NS: not significant ; r : correlation coefficient ; ΔIC: change in inspiratory capacity after bronchodilator administration; Δ respiratory parameters: change in respiratory function parameters after bronchodilator administration.

Figure 13 shows correlations between the change of IC and the change of respiratory function parameters after bronchodilator administration.

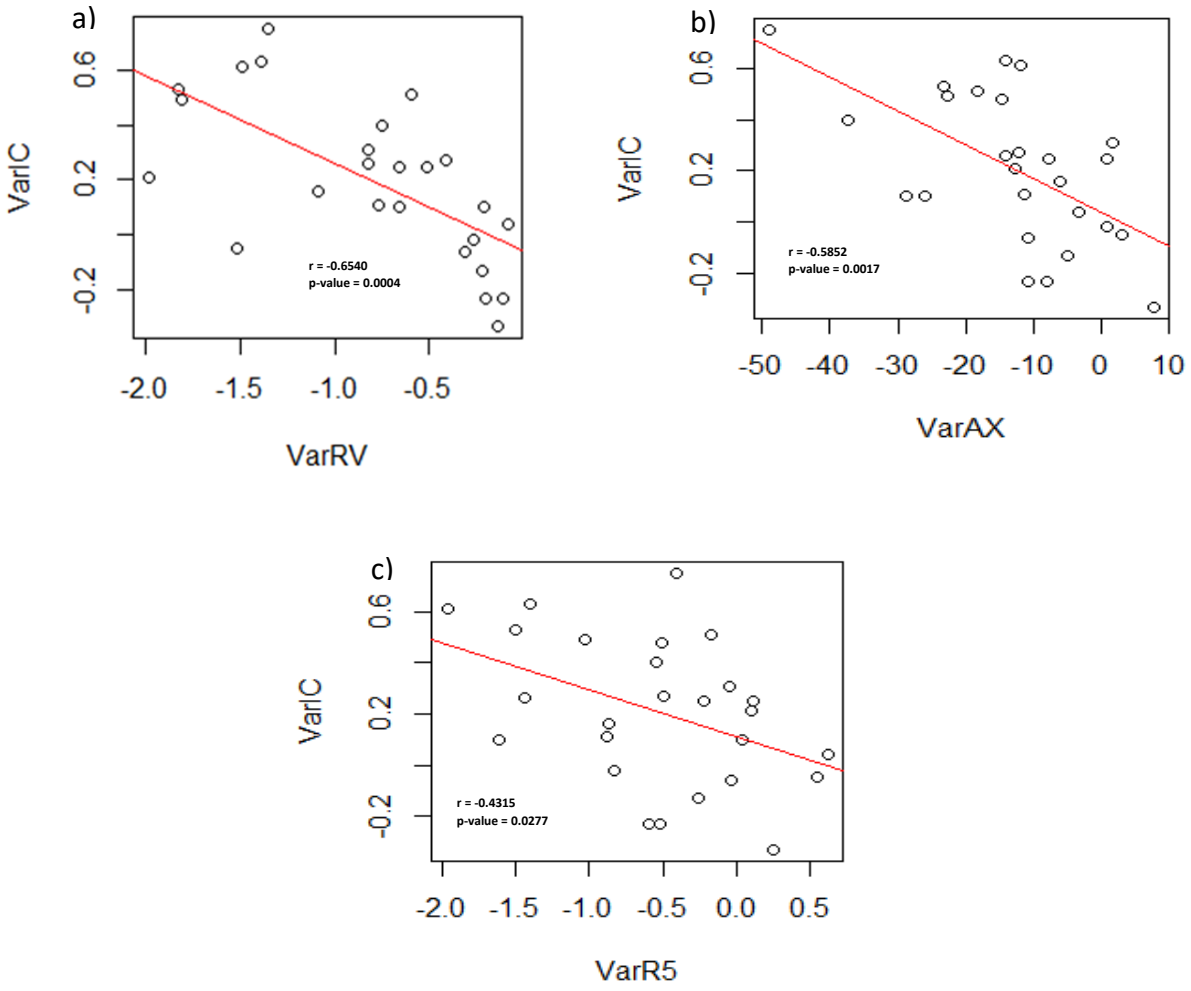

Figure 13. Correlations between the change of inspiratory capacity and the change of respiratory function parameters after bronchodilator administration. Abbreviations: VarIC: change in inspiratory capacity ; VarRV: change in residual volume ; VarAX: change in area above the reactance-frequency curve at 5Hz ; VarR5: change in resistance at 5Hz ; r : correlation coefficient.

4.7. Correlations between the changes of forced expiratory volume in one second and the changes of other respiratory function parameters after bronchodilator administration

Table 8. Correlations between the change in forced expiratory volume in one second (ΔFEV_1) and the change in respiratory functions parameters (Δ respiratory parameters) after bronchodilator administration.

	Δ FEV_1	
	r	**p-value**
Δ Respiratory parameters		
FVC (L)	0,58	<0,01
VC (L)	0,48	<0,05
IC (L)	0,20	NS
TGV (L)	-0,28	NS
TLC (L)	0,48	NS
RV (L)	-0,32	NS
RAW (cmH2O/L/S)	-0,28	NS
R5 ($cmH_2O.s/L$)	-0,40	<0,05
R19 ($cmH_2O.s/L$)	-0,19	NS
R5-19 ($cmH_2O.s/L$)	-0,39	<0,05
R5,in ($cmH_2O.s/L$)	-0,46	<0,05
R5,ex ($cmH_2O.s/L$)	-0,29	NS
X5 ($cmH_2O.s/L$)	0,37	NS
AX5 (cmH_2O/L)	-0,48	<0,05
ΔX5 ($cmH_2O.s/L$)	-0,29	NS
X5,in ($cmH_2O.s/L$)	0,41	<0,05
X5,ex ($cmH_2O.s/L$)	0,37	NS

Abbreviations: BD: bronchodilator ; FEV1: forced expiratory volume in one second ; FVC: forced vital capacity ; VC: vital capacity ; IC: inspiratory capacity ; TGV: thoracic gas volume ; TLC: total lung capacity ; RV: residual volume ; RAW: airway resistance ; R5: resistance at 5Hz ; R19: resistance at 19Hz ; R5-19: difference in resistance between 5 and 19Hz ; R5in: inspiratory resistance at 5Hz ; R5ex: expiratory resistance at 5Hz ; X5: reactance at 5Hz ; AX5: area above the reactance-frequency curve at 5Hz ; ΔX5: difference between inspiratory

and expiratory reactance at 5Hz ; X5ex: expiratory reactance at 5Hz ; X5in: inspiratory reactance at 5Hz ; NS: not significant ; r : correlation coefficient ; ΔFEV₁: change in forced expiratory volume in one second ; Δ respiratory parameters: change in respiratory function parameters.

Table 8 describes the correlations between the variation of FEV_1 and the variation of the respiratory function parameters after bronchodilator administration. The change in FVC, VC, R5, R5-19, R5in, AX5 and X5in were significantly correlated with the change in FEV_1.

Figure 14 shows correlations between the changes of FEV_1 and the change of respiratory function parameters after bronchodilator administration.

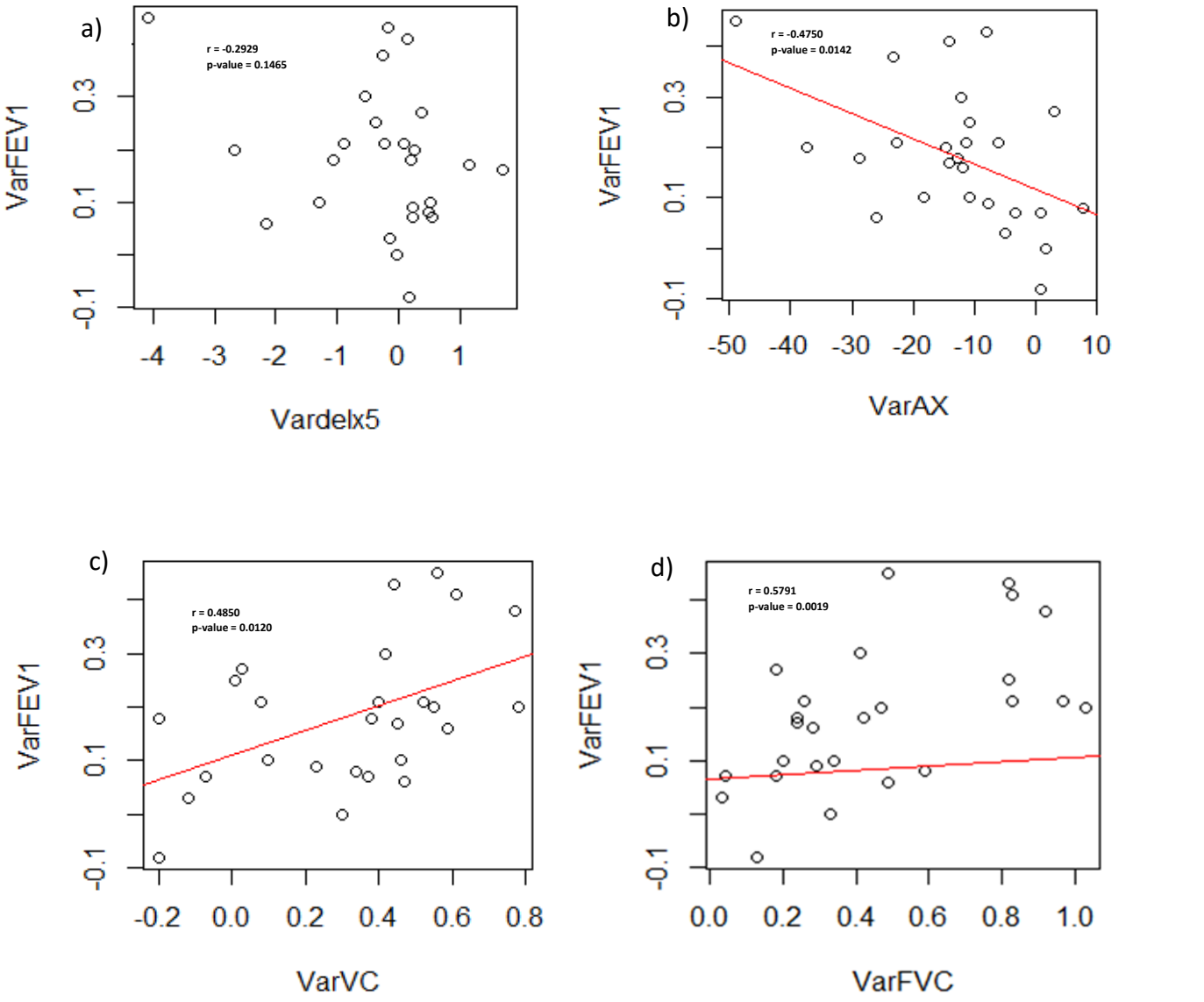

Figure 14. Correlations between the change in forced expiratory volume in one second and the change in respiratory function parameters. Abbreviations: VarFEV1: change in forced expiratory volume in one second ; VardelX5 : Variation of the difference between inspiratory and expiratory reactance at 5Hz ; VarAX: change in area above the reactance-frequency curve at 5Hz ; VarVC: change in vital capacity ; VarFVC: change in forced vital capacity ; r : correlation coefficient.

4.8. Predictors of significant IC improvement after bronchodilator administration

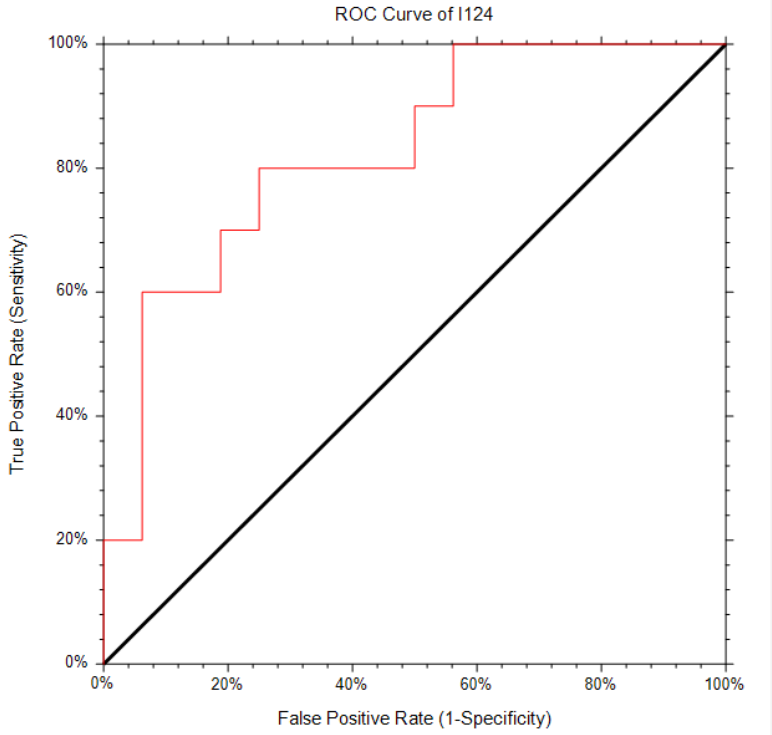

Figure 15. ROC curve for the prediction of an improvement of 10% predicted in IC. Curve represents this evaluation with the change in slow vital capacity after bronchodilator administration. Abbreviations: ROC: receiver operating characteristic ; IC: inspiratory capacity.

Figure 15 represents ROC curve for the evaluation of the prediction of a 10% improvement in IC from changes in vital capacity parameters after bronchodilator administration.

Table 9 describes the different values of the ROC-AUC and p-values. As can be seen, the variation of TGV, sRAW and VC were predictors of a 10% predicted improvement in IC.

Table 9. AUC for ROC curves and p-value results of the figure 15.

Parameters	AUC	p-value
TGV	0,74	<0,05
TLC	0,66	NS
RAW	0,68	NS
sRAW	0,80	<0,001
VC	0,82	<0,001
FVC	0,63	NS
FEV1	0,62	NS
FEV1/FVC	0,61	NS

Abbreviations: AUC: area under the curve ; TGV: thoracic gas volume ; TLC: total lung capacity ; RAW: airway resistance ; sRAW: specific airway resistance ; VC: vital capacity ; FVC: forced vital capacity ; FEV1: forced expiratory volume in one second.

Figure 16 represents the ROC curve for the evaluation of the prediction of a 10% predicted improvement in IC from changes in area above the reactance-frequency curve at 5Hz after bronchodilator administration.

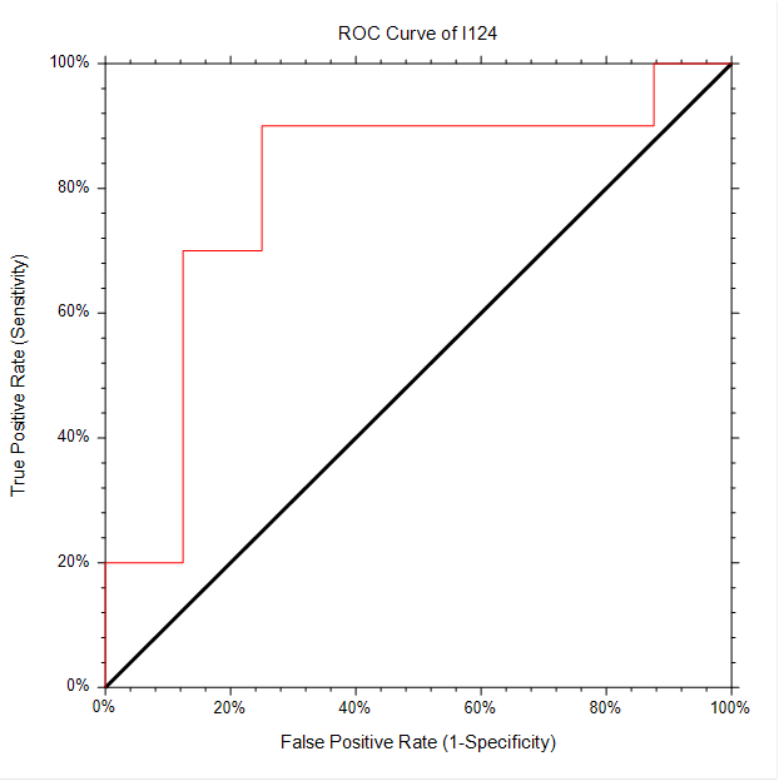

Figure 16. ROC curves for the prediction of an improvement of a 10% predicted in IC. Curve represents this evaluation with the changes in area above the reactance-frequency curve at 5Hz after bronchodilator administration. Abbreviations: ROC: receiver operating characteristic ; IC: inspiratory capacity.

Table 10. AUC for ROC curve and p-value results of the figure 16.

Parameters	AUC	p-value
X5	0,59	NS
X5,in	0,59	NS
X5,ex	0,69	<0,05
R5	0,69	<0 ,05
R5,in	0,75	<0,01
R5,ex	0,58	NS
R19	0,59	NS
R19,in	0,61	NS
R19,ex	0,60	NS
R5-19	0,68	<0,05
R5-19,in	0,72	<0,05
R5-19,ex	0,59	NS
AX5	0,80	<0,01
ΔX5	0,49	NS

Abbreviations: AUC: area under the curve ; X5: reactance of the respiratory system at 5Hz ; X5ex: expiratory reactance at 5Hz ; X5in: inspiratory reactance at 5Hz ; R5: resistance of the respiratory system at 5Hz ; R19: resistance of the respiratory system at 19Hz ; R5-19: difference in resistance between 5 and 19Hz ; R5in: inspiratory resistance at 5Hz ; R5ex: expiratory resistance at 5Hz ; R19in: inspiratory resistance at 19Hz ; R19ex: expiratory resistance at 19Hz ; R5-19in: difference in inspiratory resistance between 5 and 19Hz ; R5-19ex: difference in expiratory resistance between 5 and 19Hz ; AX5: area above the reactance-frequency curve at 5Hz ; ΔX5: difference between inspiratory and expiratory reactance at 5Hz.

Table 10 describes the different values of AUC and p-value of the figure 16. As can be seen, the variation of X5ex, R5, R5in, R5-19, R5-19in and AX5 were significant predictors of an improvement of 10% predicted in IC.

5. Discussion

Assessing the response to bronchodilator in COPD patients is supposedly important for adapting the bronchodilator therapy in patients with COPD in order to control dyspnea as best as possible. However, the relationship between FEV_1 and dyspnea has been shown to be poor. Accordingly, we were interested in studying

- the relationship between dyspnea and forced oscillation parameters;
- the relationship between the bronchodilator response of these parameters with that of FEV_1 and IC, a parameter that has been shown to be more closely related to dyspnea;
- the predictors of a clinically meaningful improvement in IC (10% predicted increase) after bronchodilation [33] .

In the following discussion, we will discuss the results of the present study. First of all, we will discuss about the assessment of the bronchodilator response after the inhalation of DUOVENT HFA®. This part of the discussion will be subdivided in two different points, the first one will be about the conventional respiratory function parameters and the second about the FOT parameters, including resistance and reactance parameters.

The second part of the discussion concerns the correlation between intensity of dyspnea, respiratory function parameters and FOT parameters.

Thirdly, we will discuss about the correlation between variation of IC and variation of respiratory function parameters. The fourth part will talk the correlation between variation of FEV_1 and variation of respiratory function parameters as this is still the most used criteria to assess the bronchodilator response in pulmonary function labs.

Finally, we will finish this discussion with the parameters that can predict a clinically meaningful improvement in inspiratory capacity.

5.1. Assessment of the bronchodilator response

5.1.1. Conventional respiratory function

As expected, the effects of the short-acting bronchodilator administration that we observed in the present study were similar to those reported in other studies [3 25 34]. Indeed, mean values of classical pulmonary function tests parameters, FEV_1, %FEV1, FVC, %FVC, VC, %VC, IC, %IC, TGV, %TGV, TLC, %TLC, RV, %RV, RAW, %RAW, sRAW and %sRAW were significantly improved after the DUOVENT HFA® inhalation (see table 4).

Bronchodilator inhalation induced a highly significant increased FEV_1 and FVC but no change for the Tiffeneau index which was concordant with previous studies [34 35]. The increase in VC is associated with a decreased RV, which is related to a reduction in air trapping after bronchodilator administration. The improvement in FEV_1 is related to an improvement in large airways resistance, as well as in airway resistance from alveolar units with rapid time constants for lung emptying.

Because bronchodilators induce rapid relaxation of airway smooth muscle and thus increase airway calibre, it was expected to observe a reduction in RAW and sRAW [17].

The significant increased IC and decreased FRC extended results of previous studies [35].

This decrease in FRC means reduced EELV, it allows patients to do exercise for longer time before dynamic hyperinflation reaches the critical point where the inspiratory reserve decreases inducing intolerable dyspnea [17]. The reduced FRC which also explains an increase in IC is the main reason for the relief of dyspnea after bronchodilator administration.

Conventional respiratory function cannot measure easily the improvement of small airways. But reduced lung volumes is a consequence of enhanced gas emptying in the alveolar units with slower mechanical time constants providing indirect evidence of a positive effect of the DUOVENT HFA® on small airway function [12].

5.1.2. Forced oscillation technique

Usually, bronchodilator effect is assessed by the changes in FEV_1. But thanks to its many advantages, FOT, is an attractive tool to evaluate the response to bronchodilator [36]. Moreover, FOT is able to assess the improvement in small airway function induced by bronchodilatation and may thus give additional information as compared to conventional respiratory function tests.

In this study, we were particularly interested about the reactance parameters which have been relatively forgotten as compared to the resistance parameters in the literature.

The changes after the inhalation of bronchodilator for the FOT parameters are shown in table 5.

5.1.2.1. Resistance

Means values of FOT parameters R5, R5-19, R5in, R5ex, R19in, R5-19in and R5-19ex were significantly improved after the bronchodilator inhalation (see table 5). This is coherent with those of the literature [17 36 37].

Compared to conventional respiratory function test, FOT gives information about the small airways. Indeed, R5 represents total airway resistance and R19 the resistance of the upper airways. Subtracting R19 from R5 (R5-19) provides an assessment of small airway resistance [21 23]. As we know, small airways are the most impacted in COPD as discussed in the introduction. As we can see, R5 values were much higher than R19 values meaning an increased small airway resistance.

As can be seen in table 5, inhaled bronchodilators decrease both total and small airways resistance significantly. But conversely, no significant decrease for the R19 parameter. This suggest that as expected, the bronchodilator had no significant effect on the upper airway resistance.

5.1.2.2. Reactance

The changes in reactance parameters observed after bronchodilator administration in the present study were also in accordance with the literature [27 34 37]. Mean values of X5, AX5, X5in, X5ex were significantly improved (i.e. became less negative) after bronchodilator administration (see table 5). Given that reactance values reflect the elastic properties of the system and that elastic properties are correlated with the small airways, reactance values are correlated with small airways. Thus, a decrease in AX5 and an increase in X5 means that we had an improvement in small airways function. Less negative reactance values mean that there was a decrease of the hyperinflation and thus improvement of dyspnea. In others words, less negative reactance values mean that the disease became less severe [20 21].

On the other hand, the parameter ΔX5 didn't improve significantly as opposed to our initial study hypothesis. This result is in accordance with a recent study directed by Stephen Milne at al [3]. In parallel only one patient experienced a relief of tidal respiration EFL according to the criteria of Dellacà after bronchodilation [38 39]. This means that despite the improvement in maximal expiratory flows, tidal EFL probably rarely disappear after bronchodilator administration in COPD. Accordingly, changes in ΔX5 are not sensitive to the effect of bronchodilators in COPD.

However, the present study suggests that other reactance parameters change after bronchodilator administration could be of interest. For example, AX5 (the area above the reactance-frequency curve) showed dramatic improvement. As discussed in the literature, changes in AX5 are correlated to the changes in the degree of peripheral airway obstruction

thus it is correlated to R5-19 [21]. The highly significant decrease in AX5 ($p<0,001$) show that there is a decrease in peripheral airways obstruction after the administration of the bronchodilator inducing an improvement of dyspnea. Moreover, as discussed below, AX5 was correlated with dyspnea and the changes in AX5 after bronchodilator administration were correlated with those of IC.

As described in the literature, expiratory reactance as well as resistance parameters were more severely impaired in the expiratory than the inspiratory part of the breathing cycle (see table 5) [25] [40]. This is due to a higher pleural pressure in expiration explaining a reduced small airway diameter at a given lung volume in the expiratory phase of the breathing cycle. Higher reactance might be explained by the presence of EFL in expiration rather than in inspiration. The improvement of parameters measured during inspiration appeared to be higher than those measured in expiration after the administration of the bronchodilator. This was particularly true for R5 and R5-R19. This might suggest that the changes in the bronchial smooth muscle tone have more effect on the airway diameter in the inspiratory phase.

5.2. Correlation between intensity of dyspnea, conventional respiratory function and FOT parameters

Two questionnaires were used to evaluate the correlation between the intensity of dyspnea and the different respiratory parameters in this study: the mMRC questionnaire and the San Diego SOBQ. We will discuss both.

We only analysed the correlations in post-bronchodilator condition as these instruments assess dyspnea in the daily life. We indeed postulated that in the daily life, patients are under the influence of the bronchodilators with which they are treated on a regular basis.

5.2.1. mMRC questionnaire

This study could not find any correlation between the intensity of dyspnea assessed by the mMRC questionnaire and pulmonary function test parameters. This might be due to the fact that this questionnaire is only a 5 scale score not very sensitive to changes in dyspnea intensity. This probably explains the fact that a majority of the patients complained of a mMRC dyspnea score of 2 or 3 on this scale.

5.2.2. San Diego shortness of breath questionnaire

Previous study showed that this questionnaire was a valuable tool to assess dyspnea [41]. We found some correlations between the intensity of dyspnea assessed by the San Diego SOBQ questionnaire and pulmonary function parameters. This questionnaire appeared to be more discriminant for the assessment of dyspnea intensity. This can be due to the fact that it was more extensive. The dyspnea on this scale scores had a more widespread distribution and thus was more exploitable.

As can be seen in table 6, dyspnea assessed by the San Diego SOBQ significantly correlated with R5, R5ex, IC, X5, RAW, R5-19 and AX5.

In accordance with the literature, we found a significant correlation between the dyspnea score and IC but no correlation with FEV_1 (see figure 12) [26]. Interestingly, Boni et al. also showed that changes in IC after bronchodilators in patients with COPD and EFL were strongly correlated with an improvement of dyspnea, even in the absence of a significant increase in FEV_1 [33]. Other studies also demonstrated a significant association between improvements in dyspnea and the increase in IC following bronchodilator administration [35 42]. The present study confirmed that IC is more closely related to dyspnea than FEV_1.

We also found a correlation between FOT parameters and dyspnea. All these parameters are thought to be related to small airway function. According to our knowledge, this study is the first to show a significant correlation between FOT parameters and dyspnea.

5.3. Correlation between variation of inspiratory capacity and variation of respiratory function parameters

Given there is a strong correlation between IC and dyspnea as well as between changes in IC and changes in dyspnea, we wanted to assess the correlation between changes in IC and those of various respiratory function parameters after bronchodilator administration in order to propose clinically useful parameters to assess during a bronchodilator test.

We found that the strongest correlation with variation of IC was the variation of RV (p-value <0,001) (see table 7-figure 13 A). This could be expected since both an increase in IC and a reduction in RV reflect reduced air trapping and lung hyperinflation [3].

The finding of a significant association between the changes of IC and those of AX5 and R5 is interesting (see table 7-figure 13 B-C). Milne et al. had shown that the changes in hyperinflation described in their study as Δ(RV/TLC) was highly significantly correlated with the changes in AX5 reinforcing our results. They also shown a significant correlation between changes in hyperinflation with changes in R5 like we have found [3].

Our results were concordant with those of the study of Milne et al., with the difference that we had more patients recruited and including more severe cases.

However, we could not find any correlation with the changes in FEV_1, suggesting that IC and FEV_1 reflect different aspects of airway function.

The association however was not strong, the changes in FOT parameters explaining less than 35% of the changes in IC.

5.4. Correlation between variation of forced expiratory volume in one second and variation of respiratory function parameters

The strongest correlation between variation of FEV_1 was with the variation of FVC (p-value <0,01) (see table 8-figure 14 D).

Although we also found some association between changes in FEV_1 and changes in FOT parameters, the association was weaker than for the association with the changes in IC (see table 7 and table 8).

5.5. Prediction of clinically meaningful improvement in inspiratory capacity

Given that correlation between IC and dyspnea. It was logical to determine which parameters could be predictor of an improvement of IC and thus a predictor of an improvement of dyspnea.

The predictors of an improvement of 10% for the IC were determined by ROC curves. The reason for this improvement threshold was determined by previous studies. Indeed, Boni et al., showed that for patients with an increase in IC greater than 10% of the predicted value, there was a significant decrease in exertional dyspnea, owing to a decreased EELV allowing for an improved exercise endurance [33 35].

This study suggested that some changes observed after bronchodilator administration can predict a significant increase in IC.

Two parameters were particularly accurate predictors: the changes in VC (AUC=0,82, p-value <0,001) for the conventional parameter and AX5 (AUC=0,80, p-value <0,01) for the FOT parameters (see figure 15 and 16). As the AUC of the ROC curve for AX5 was superior to 0,70, it can be considered as a good predictor for a significant improvement in IC [43]. AX5 appears particularly interesting as it can be measured during tidal breathing and without any forceful maneuver, as opposed to IC or VC.

As opposed to our initial hypothesis, ΔX5 was not a predictor for a significant improvement in IC (see table 10).

6. Study limitations

This study had some limitations. First of all, the Tremoflo® was sometimes very sensitive hence the need to repeat the manoeuvres several times.

Secondly, this study only analysed 26 patients which is a small cohort and the results presented should be confirmed in a larger cohort.

Still regarding patient limitations, the length of the tests could also influence the results. Indeed, some of these 26 patients have lost patience and therefore gave poorer results as the length of tests increased. It is also important to notice that for some patients it was difficult to stay in the plethysmograph, they could also provide poorer results, which reinforces the potential for the use of FOT, which does not require any unusual breathing maneuver.

Another limitation was the calculation of the Fres and AX5 parameters because in some cases, the Fres was upper than 37 Hz (the upper frequency sent by the Tremoflo®), thus the program could not exactly determine it. Although this somewhat impacted the calculation of the AX5, it does not preclude this index to increase when Fres increased above the frequency allowed by the Tremoflo®.

We did not assess the reproducibility of the bronchodilation response of the FOT parameters, which is a limitation of the present work. It is known that the day to day reproducibility of bronchodilator response assessed by changes in FEV_1 is poor [17]. This latter is not knowing for FOT parameters in COPD patients. Therefore, it would be important to evaluate it as we would like to use this test to assess improvement of dyspnea after bronchodilator administration in clinic practice.

7. Conclusion and perspectives

This study evaluated the bronchodilator response after the administration of DUOVENT HFA®. It compared this response both with conventional respiratory function tests and FOT parameters.

This study suggests that FOT parameters can be useful in the assessment of the bronchodilator response. This is particularly true for AX5, a parameter that has been shown to be associated with small airway function. It appears to be a promising index since we found that it was related to dyspnea and IC and that the changes in AX5 after bronchodilator administration were related to those of IC and were a good predictor of significant changes in IC.

These results need to be confirmed in a larger cohort. Moreover, the reproducibility of changes in FOT parameters after bronchodilatation needs to be assessed.

In conclusion, according to its ability to assess small airway function, FOT gives additional information as compared to conventional respiratory function. Since FOT has several advantages compared to other techniques, particularly its ease of use and minimal patient cooperation required, it is a promising method to assess bronchodilator response in patients with COPD.

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Annex 1

Évaluation de la pertinence de la technique des oscillations forcées pour évaluer la réponse aux bronchodilatateurs chez des sujets souffrant de BPCO.

Promoteur de l'étude : Professeur Eric Marchand URPhyM Faculté de Médecine-UNamur. Rue de Bruxelles, 61 5000 Namur - Service de Pneumologie CHU-UCL-Namur Site de Godinne 1, Avenue du Docteur Therasse 5530 Yvoir.

Comité d'éthique Médicale : CHU-UCL Namur

Médecins investigateurs locaux : Professeur Eric Marchand.
Laboratoire de Physiologie respiratoire, URPhyM, Faculté de Médecine-UNamur. Rue de Bruxelles, 61, 5000 Namur.
Service de Pneumologie, CHU-UCL-Namur, Site de Godinne Avenue du Docteur Therasse,1, 5530 Yvoir.

I. Information essentielle à votre décision de participer

Introduction :

Vous êtes invité à participer à une étude clinique destinée à évaluer l'intérêt de la technique des oscillations forcées pour évaluer la réponse aux bronchodilatateurs chez les patients atteints de bronchopneumopathie chronique obstructive (BPCO).

Le médecin investigateur espère que cette étude clinique pourra apporter

- une meilleure définition des paramètres utiles à évaluer lors d'un test de bronchodilatation
- une meilleure compréhension des liens entre l'effet des bronchodilatateurs sur l'essoufflement et sur les tests respiratoires.

Avant que vous n'acceptiez d'y participer, nous vous invitons à prendre connaissance de ses implications en termes d'organisation, avantages et risques éventuels (dans le cas de cette étude il n'y a pas de risque significatif si vous bénéficiez déjà d'un traitement bronchodilatateur), afin que vous puissiez prendre une décision en toute connaissance de cause. Ceci s'appelle donner un « consentement éclairé ».

Veuillez lire attentivement ces informations et poser toutes les questions que vous souhaitez à l'investigateur ou à la personne qui le représente. Ce document comprend 3 parties : l'information essentielle à votre prise de décision, votre consentement écrit et des informations complémentaires (annexes) qui détaillent certaines parties de l'information de base.

Si vous participez à cette étude clinique, vous devez savoir que :

- Cette étude clinique est mise en œuvre après évaluation par un comité d'éthique.
- Votre participation est **volontaire** et doit rester **libre de toute contrainte**. Elle nécessite la signature d'un document exprimant votre consentement. *Même après l'avoir signé, vous pouvez*

arrêter de participer en informant le médecin investigateur. Votre décision de ne pas ou de ne plus participer à l'étude n'aura aucun impact sur la qualité de vos soins ni sur vos relations avec le médecin investigateur.

- Les données recueillies à cette occasion sont **confidentielles** et votre **anonymat** est garanti lors de la publication des résultats.
- Une **assurance** a été souscrite au cas où vous subiriez un dommage lié à votre participation à cette étude clinique.
- **Aucun frais** supplémentaire ne vous sera facturé pour les visites, examens ou traitements **dans le cadre de cette étude**. Par facilité cependant, votre participation vous sera sans doute proposée en lien avec un rendez-vous de consultation prévu. Dans ce cas, les honoraires liés à la consultation et aux examens liés à celle-ci seront facturés et pris en charge par votre mutuelle de manière habituelle.
- Vous pouvez toujours contacter le médecin investigateur ou un membre de son équipe si vous avez besoin d'informations complémentaires.
- Il se pourrait qu'à l'avenir, des données recueillies au cours de cette étude puisse être d'intérêt pour une analyse relative à une ou plusieurs autres études scientifiques. Nous vous demandons sur le formulaire de consentement votre accord pour cette utilisation ultérieure des données. Si les données relatives à votre participation devaient être analysées par des personnes tierces aux investigateurs de la présente étude, elles seraient transmises de manière strictement anonyme.

Un complément d'informations sur vos « Droits de participant à une étude clinique » est fourni en annexe.

Objectifs et description du protocole de l'étude :

Nous vous proposons de participer à une étude clinique portant sur **l'évaluation de la pertinence de la technique des oscillations forcées pour évaluer la réponse aux bronchodilatateurs chez des sujets souffrant de BPCO** qui devrait inclure entre 20 à 80 patients. L'étude est menée uniquement au CHU-UCL-Namur.

Le but est d'évaluer :

- L'objectif principal de l'étude est d'évaluer si les mesures de la fonction pulmonaire enregistrés en respiration normale avec la TOF sont capables de prédire un effet sur la distension du poumon après l'administration d'un.
- En outre, les autres objectifs de la présente étude sont les suivants:
  - comparer la capacité des mesures par TOF à prédire une réduction de la distension des poumons après l'administration d'un bronchodilatateur avec celle de mesures plus classiques de la fonction pulmonaire;
  - comparer la variation de la distension des poumons induite par l'administration d'un bronchodilatateur avec les modifications induites pour d'autres mesures de fonction respiratoire par TOF et mesures plus classiques de la fonction pulmonaire;
  - évaluer la relation entre l'efficacité du traitement bronchodilatateur perçue par le patient et divers paramètres des tests respiratoires.
  - évaluer la relation existant entre essoufflement et divers paramètres des tests respiratoires, en particulier mesurés par TOF.

Les critères d'inclusion dans l'études sont :

- Diagnostic clinique de BPCO confirmé par les tests fonctionnels respiratoires

- Tabagisme ancien ou actif (un minimum est requis).
- Age > 40 ans.
- Consentement éclairé.

Les critères d'exclusion de l'étude sont :

- Incapacité à effectuer les tests d'EFR;
- Besoin d'oxygénothérapie continue;
- Glaucome à angle fermé;
- Antécédent de rétention urinaire;
- Grossesse.

Déroulement de l'étude :

Si vous remplissez les critères pour être inclus dans l'étude et acceptez de participer à l'étude, vous serez soumis aux tests et examens décrits ci-dessous.

Votre participation se fera au cour d'**une seule et unique visite** d'une durée de environ **1h30 à 2h00** au cours de laquelle nous vous pèserons, mesurerons. De brefs questionnaires relatifs à votre essoufflement vous seront soumis avant les mesures respiratoires.

Il vous sera demandé de suspendre vos traitements bronchodilatateurs inhalés pour minimum 6 à 24 heures (selon le type de bronchodilatateur utilisé) avant les mesures.

Si vous êtes fumeur, il vous sera également demandé de ne pas fumer dans les 4 heures précédant la visite consacrée à l'étude.

1. **Mesures par technique des oscillations forcées**

Les mesures seront réalisées à l'aide d'un appareil qui permet de générer un train de petites ondes de pressions à peine perceptible et, ainsi, de mesurer l'obstacle que représente votre système respiratoire à la pénétration des ondes à l'intérieur de celui-ci. Les mesures sont effectuées lorsque vous respirez normalement par la bouche à travers le système, sans effort particulier, nez occlus par un pince-nez pour éviter les fuites d'air, les joues soutenues par les mains (les vôtres ou celles d'un opérateur afin de réduire l'influence de l'élasticité des joues sur les mesures réalisées). L'appareil enregistre divers paramètres liés à votre respiration et aux modifications très discrètes induites par la vague de petites ondes de pression qu'il génère.

2. **La spirométrie**

Cet examen très simple permet la mesure des volumes et des débits pulmonaires. Il consiste à souffler dans une embout relié à un capteur. Celui-ci permet, en fonction de la "puissance" de votre souffle, d'enregistrer à la fois la "capacité" de votre poumon (c'est-à-dire le volume d'air que vos poumons peuvent inspirer et expirer) et le débit de votre souffle (c'est-à-dire le volume maximum d'air que vous pouvez expirer en une seconde = VEMS).
Pour éviter les fuites d'air, on place préalablement un pince-nez. La manœuvre consiste à respirer normalement dans l'embout, puis au signal, de prendre une inspiration profonde et maximale, suivie d'une expiration complète et rapide en vidant le plus vite et le plus complètement possible vos poumons. Trois manœuvres acceptables au moins sont réalisées dans chaque position. Si vous souffrez de BPCO, vous êtes habitués à ce test qui est le plus fréquemment réalisé au laboratoire d'épreuves fonctionnelles respiratoires.

3. La pléthysmographie

C'est un examen quasiment similaire au précédent sauf qu'il se passe dans une cabine en verre. Il permet la mesure du volume d'air qui reste dans vos poumons à la fin d'une expiration et des résistances

bronchiques. Plus les bronches sont réduites de calibres et plus leur résistance à l'écoulement de l'air est augmentée.
Cette mesure nécessite la fermeture hermétique de la porte de la cabine. La communication entre vous et le technicien se fait alors par l'intermédiaire d'un microphone.
Comme pour la spirométrie, on place un embout buccal et un pince-nez afin d'éviter les fuites d'air lors de l'expiration. Le technicien vous demande alors d'effectuer les manœuvres d'inspiration et d'expiration. L'appareil enregistre alors les résistances puis les volumes d'air persistant dans le poumon en fin d'expiration en bloquant une fraction de seconde l'inspiration ou l'expiration. Deux mesures au moins seront réalisées.

L'ensemble des données et mesures recueillies le seront soit par le médecin investigateur, soit par un représentant (infirmière de recherche) ou mémorant-e (étudiant-e en Master de Sciences biomédicales), formés aux techniques de fonction respiratoire, sous la responsabilité du médecin investigateur.

Risques liés à votre participation à l'étude :

Les examens tels que proposés dans cette étude ne présentent aucun risque significatif pour la santé.

Vous pouvez ressentir un peu d'essoufflement après une spirométrie mais l'examen ne comporte pas de risque particulier dans les conditions d'inclusion de l'étude.

La technique des oscillations forcées est encore moins susceptible de générer d'effets indésirables car elle ne nécessite aucune manœuvre particulière. Vous ressentirez à peine les modifications de pression générées par l'appareil au niveau de la bouche. Il faut insister sur le fait que l'onde de pression est liée à la compression de l'air ambiant, il ne s'agit nullement d'ondes toxiques ou dangereuses ; aucune substance étrangère ou autre agent n'est introduit dans vos voies respiratoires lors de ces mesures par oscillations forcées.

L'administration de DUOVENT est le plus souvent très bien tolérée et induit même habituellement une diminution de l'essoufflement. Il s'agit d'un médicament habituellement recommandé dans le traitement de la BPCO. De rares effets secondaires peuvent toutefois survenir: augmentation de la fréquence cardiaque, tremblements, sécheresse de bouche pour citer les plus fréquents. Le DUOVENT est déconseillé en cas de glaucome (un type de glaucome seulement) et de problèmes sérieux de prostate qui sont des critères d'exclusion à la participation dans l'étude.

Bénéfices :

Vous ne devez pas attendre d'autres bénéfices que la satisfaction d'avoir participé à une meilleure compréhension de certains aspects de votre fonction respiratoire ou de votre maladie.

Retrait de l'étude :

Attention : Il y a lieu de distinguer « retrait de l'étude » et « retrait du consentement ».

Retrait de l'étude signifie simplement que le patient arrête sa participation avant que l'ensemble des mesures aient été réalisées.

Cela ne veut pas dire qu'il retire son consentement à l'analyse des données collectées.

Retrait du consentement à l'étude signifie effectivement retirer son consentement à sa participation à l'étude sans justification à donner et cela peut vouloir dire retirer son consentement au traitement des données recueillies dans le cadre de l'étude.

Votre participation est volontaire et vous avez le droit de vous retirer de l'étude pour quelque raison que ce soit, sans devoir vous justifier. Néanmoins, le médecin investigateur ou son représentant vous demanderont si vous consentez à l'analyse des données jusque-là recueillies.

Si vous participez à cette étude clinique, nous vous demandons :

- De collaborer pleinement au bon déroulement de cette recherche.
- De ne masquer aucune information relative à votre état de santé, aux médicaments que vous prenez ou aux symptômes que vous ressentez.

Vous devez également savoir que les données recueillies au cours de cette étude pouvant être d'intérêt pour votre suivi médical, les éléments pertinents seront transmis à votre médecin traitant sauf si vous y opposez.

Contact :

Si vous avez besoin d'informations complémentaires, mais aussi en cas de problème ou d'inquiétude, vous pouvez contacter le médecin investigateur (Marchand, Eric) au numéro de téléphone suivant : 081/ 72 43 43 ou 081/ 42 33 61 **ou** un membre de son équipe de recherche (Boulanger, Sarah) au numéro de téléphone suivant (081/ 72 43 05).

Si vous avez des questions relatives à vos droits de participant à une étude clinique, vous pouvez contacter le médiateur des droits du patient de votre institution (Madame Brigitte Malhomme) via le numéro de téléphone: 081 / 42 30 30. Si nécessaire, ce dernier peut vous mettre en contact avec le comité d'éthique.

II. Consentement éclairé

Participant

1. Je déclare que j'ai été informé sur la nature de l'étude, son but, sa durée, les éventuels bénéfices et risques et ce que l'on attend de moi. J'ai pris connaissance du document d'information et des annexes à ce document.
2. J'ai eu suffisamment de temps pour y réfléchir et en parler avec une personne de mon choix comme mon médecin généraliste ou un membre de ma famille.
3. J'ai eu l'occasion de poser toutes les questions qui me sont venues à l'esprit et j'ai obtenu une réponse satisfaisante à mes questions.
4. J'ai compris que ma participation à cette étude est volontaire et que je suis libre de mettre fin à ma participation à cette étude sans que cela ne modifie mes relations avec l'équipe thérapeutique en charge de ma santé.
5. J'ai compris que des données me concernant seront récoltées pendant toute ma participation à cette étude et que le médecin investigateur et le promoteur de l'étude se portent garant de la confidentialité de ces données.
6. Je donne mon accord pour que les données récoltées au cours de cette étude soient utilisées de façon anonyme dans le cadre d'autre études concernant les mesures d'oscillations forcées ou la BPCO. Dans le cas inverse, veuillez biffer le point 6.

Votre médecin traitant sera informé des résultats des résultats des tests respiratoires conventionnels (spirométrie), sauf objection de votre part.

J'ai reçu une copie de l'information au participant et du consentement éclairé.

Nom, prénom, date, lieu et signature (Lu et Approuvé) :

Médecin investigateur :

Je soussigné, **Marchand Eric** médecin investigateur confirme avoir fourni oralement les informations nécessaires sur l'étude et avoir fourni un exemplaire du document d'information au participant.

Je confirme qu'aucune pression n'a été exercée pour que le patient accepte de participer à l'étude et que je suis prêt à répondre à toutes les questions supplémentaires, le cas échéant.

Je confirme travailler en accord avec les principes éthiques énoncés dans la dernière version de la « Déclaration d'Helsinki », des « Bonnes pratiques Cliniques » et de la loi belge du 7 mai 2004, relative aux expérimentations sur la personne humaine.

Nom, prénom, Date et signature du représentant de l'investigateur :	**Marchand Eric, Date et signature du médecin investigateur :**

Évaluation de la pertinence de la technique des oscillations forcées pour évaluer la réponse aux bronchodilatateurs chez des sujets souffrant de BPCO .

Promoteur de l'étude : Professeur Eric Marchand URPHyM Faculté de Médecine-UNamur Rue de Bruxelles, 61 5000 Namur, Service de Pneumologie CHU-UCL-Namur Site de Godinne 1, Avenue du Docteur Therasse 5530 Yvoir.

Organisme de recherche : NA

Comité d'éthique Médicale : CHU-UCL Namur

Médecins investigateurs locaux : Professeur Eric Marchand.
Laboratoire de Physiologie respiratoire, URPhyM, Faculté de Médecine-UNamur. Rue de Bruxelles, 61, 5000 Namur.
Service de Pneumologie, CHU-UCL-Namur, Site de Godinne Avenue du Docteur Therasse,1, 5530 Yvoir.

Informations complémentaires

1 : Compléments d'informations sur l'organisation de l'étude :

Si vous décidez de participer à cette étude, l'entièreté des examens ou procédures à l'étude sont à charge du promoteur.

Le médecin investigateur et ses collaborateurs seront les seuls à analyser vos données. Si, plus tard, ces données devaient être utilisées dans le cadre d'autres études, le médecin investigateur s'engage à les coder de manière à ce que vous ne puissiez pas être identifié. (votre identité sera remplacée par un code d'identification dans l'étude)

L'investigateur est responsable de la collecte des données recueillies par tous les investigateurs participant à la recherche, de leur traitement et de leur protection en conformité avec les impératifs de la loi belge relative à la protection de la vie privée.

Le promoteur utilisera les données collectées, si besoin, dans le cadre de l'étude à laquelle vous participez mais souhaite également pouvoir les utiliser dans le cadre d'autres recherches concernant la même maladie que la vôtre et la technique des oscillations forcées. Toute utilisation de vos données en dehors du contexte décrit dans le présent document ne pourrait être menée qu'après approbation du comité d'éthique.

Assurance :

Toute participation à une étude clinique comprend un risque aussi petit soit-il. Le promoteur assume, même en l'absence de faute, la responsabilité du dommage causé au participant (ou en cas de décès, à ses ayants-droit) et lié de manière directe ou indirecte à sa participation à la recherche. Le promoteur a souscrit un contrat d'assurance de cette responsabilité.

Annex 2

UNIVERSITÉ DE NAMUR

QUESTIONNAIRE

Nom et prénom du patient :

_____

PROFESSEUR ERIC MARCHAND

1. ***Données personnelles :***

- ✓ Date de naissance : / /
- ✓ Age : _____
- ✓ Sexe : *Homme - Femme*
- ✓ Tabagisme : *Oui - Jamais - Ancien(ne) fumeur-se*

Nombre de cigarettes par jour : _____

Nombre de paquet par année : _____

2. ***Données anthropomorphiques :***

- ✓ *Poids : _____*
- ✓ *Taille : _____*

3. ***Données médicales :***

a) Pour patients sains :
Souffrez-vous d'une maladie respiratoire chronique ?
La ou lesquelles ; depuis quand

Souffrez-vous d'une maladie cardiaque?

La ou lesquelles ; depuis quand

b) Pour patients BPCO :
Depuis quand êtes vous soigné pour votre bronchopneumopathie chronique obstructive (bronchite chronique-emphysème) ; depuis quand avez-vous des traitements en inhalation ?

- Avez-vous présenté une dégradation de votre état respiratoire ayant nécessité la prise d'antibiotiques ou de corticostéroïdes (Medrol) au cours des 12 derniers mois ? Quand (date), combien d'épisodes ? Avec hospitalisation ? Dernier épisode dans les 15 jours ?

_____
_____

4. ***Antécédents médicaux :***

_____
_____
_____
_____
_____
_____
_____
_____
_____
_____
_____
_____
_____
_____
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_____

5. ***Antécédents chirurgicaux thoraciques :***

_____
_____
_____
_____
_____
_____
_____
_____
_____
_____
_____
_____

6. ***Traitement :***

a) Quels médicaments prenez-vous actuellement ?

_____
_____
_____
_____
_____
_____
_____

Médicaments inhalés ?

_____
_____
_____

b) A quelle heure avez-vous pris vos inhalés médicaments la dernière fois ?

1 Médicament : Date et heure

2 Médicament : Date et heure

3 Médicament : Date et heure

Annex 3

Nom: Date:

CAT™
COPD Assessment Test

Quel est l'état de votre BPCO ? Répondez au questionnaire CAT (COPD Assessment Test pour évaluer votre BPCO

Ce questionnaire vous aidera, ainsi que votre médecin, à mesurer l'impact de la BPCO sur votre bien-être et votre santé au quotidien. Vous pourrez, ainsi que votre médecin, utiliser les réponses et les scores du questionnaire pour mieux soin de votre BPCO et tirer le plus grand bénéfice de votre traitement.

Exemple: Je suis très heureux (heureuse) 0 X 2 3 4 5 Je suis très triste

			SCORE
Je ne tousse jamais	0 1 2 3 4 5	Je tousse tout le temps	
Je n'ai pas du tout de glaire (mucus) dans les poumons	0 1 2 3 4 5	J'ai la poitrine très encombrée de glaire (mucus)	
Je n'ai pas du tout la poitrine oppressée	0 1 2 3 4 5	J'ai la poitrine très serrée	
Quand je monte une côte ou une volée de marches, je ne suis pas essoufflé(e)	0 1 2 3 4 5	Quand je monte une côte ou une volée de marches, je suis très essoufflé(e)	
Je ne suis pas limité(e) dans mes activités chez moi	0 1 2 3 4 5	Je suis très limité(e) dans mes activités chez moi	
Je ne suis pas inquiet(e) quand je quitte la maison, en dépit de mes problèmes pulmonaires	0 1 2 3 4 5	Je suis très inquiet(e) quand je quitte la maison, en raison de mes problèmes pulmonaires	
Je dors bien	0 1 2 3 4 5	Je dors mal à cause de mes problèmes pulmonaires	
Je suis plein(e) d'énergie	0 1 2 3 4 5	Je n'ai pas d'énergie du tout	

Cliquez pour obtenir le total de votre score

Annex 4

Echelle de dyspnée MRC

Pas de dyspnée, sauf en cas d'effort physique important	0
Dyspnée lors de la marche rapide à plat ou en légère pente	1
A plat, dyspnée à l'origine d'une cadence plus lente par rapport aux personnes du même âge ou obligeant à faire des pauses plus fréquentes	2
Dyspnée après 100 mètres à plat ou après quelques minutes	3
Dyspnée lors de l'habillage et du déshabillage; dyspnée ne permettant plus de quitter le domicile	4

Nom et Prénom : _____

Date et heure : _____

Annex 5

CENTRE MÉDICAL DE L'UNIVERSITÉ DE CALIFORNIE (UCSD), SAN DIEGO

PROGRAMME DE RÉADAPTATION RESPIRATOIRE

QUESTIONNAIRE SUR L'ESSOUFFLEMENT

Veuillez indiquer à quel point vous êtes essoufflé(e) lorsque vous faites, ou si vous deviez faire, chacune des activités suivantes. **Ne passez aucune question.** Si vous n'avez jamais fait ou ne faites plus ce type d'activité, essayez d'évaluer au mieux à quel point vous seriez essoufflé(e) si vous deviez la faire. Veuillez lire les deux exemples ci-dessous avant de tourner la page et de commencer le questionnaire.

Lorsque je fais les activités suivantes (ou si je devais les faire), je dirais que mon essoufflement est :

0	Nul
1	
2	
3	
4	Très important
5	Maximal (ou bien je ne suis pas capable de faire l'activité à cause de mon essoufflement)

1. Me brosser les dents ..... **0 1 2 ③ 4 5**

Paul s'est senti moyennement essoufflé au cours des 7 derniers jours quand il se brossait les dents. Il a donc entouré le chiffre 3.

---

2. Tondre la pelouse ..... **0 1 2 3 4 ⑤**

Anne n'a jamais tondu la pelouse mais pense qu'elle aurait été trop essoufflée pour le faire au cours
des 7 derniers jours. Elle a donc entouré le chiffre 5.

Lorsque je fais les activités suivantes (ou si je devais les faire), je dirais que mon essoufflement est :

0	Nul
1	
2	
3	
4	Très important
5	Maximal (ou bien je ne suis pas capable de faire l'activité à cause de mon essoufflement)

1. Au

repos.....**0 1 2 3**

.....4 5

2. Marcher sur un terrain plat à mon propre

rythme **0 1 2 3**

.....4 5

3. Marcher sur un terrain plat avec d'autres personnes de mon âge

.....**0 1 2 3**
.....4 5

4. Monter une

côte.....**0 1 2 3**

.....4 5

5. Monter des

marches **0 1 2 3**

.....4 5

6. Manger **0 1 2 3**

.....4 5

7. Me lever d'une

chaise **0 1 2 3**

.....4 5

8. Me brosser les

dents.....**0 1 2 3**

.....4 5

9. Me raser et/ou me

coiffer.....**0 1 2 3**

.....4 5

10. Prendre une douche/un

bain.....**0 1 2 3**

.....4 5

Lorsque je fais les activités suivantes (ou si je devais les faire), je dirais que mon essoufflement est :

0	Nul
1	
2	
3	
4	Très important
5	Maximal (ou bien je ne suis pas capable de faire l'activité à cause de mon essoufflement)

11. M'habiller **0 1 2 3**

.....4 5

12. Ramasser des objets et les

ranger **0 1 2 3**

.....4 5

13. Faire la

vaisselle **0 1 2 3**

.....4 5

14. Balayer/passer

l'aspirateur **0 1 2 3**

.....4 5

15. Faire le

lit **0 1 2 3**

.....4 5

16. Faire les

courses **0 1 2 3**

.....4 5

17. Faire la lessive à la

main..... **0 1 2 3**

.....4 5

18. Laver la

voiture **0 1 2 3**

.....4 5

19. Tondre la

pelouse..... **0 1 2 3**

.....4 5

20. Arroser la

pelouse..... **0 1 2 3**

.....4 5

21. Activités

sexuelles..... **0 1 2 3**

.....4 5

0	Nul
1	
2	
3	
4	Très important
5	Maximal (ou bien je ne suis pas capable de faire l'activité à cause de mon essoufflement)

À quel point suis-je limité(e) dans ma vie quotidienne par :

22. Le fait d'être

essoufflé(e)..... **0 1 2 3**

.....4 5

23. La peur de me faire mal en faisant trop

d'efforts..... **0 1 2 3**

.....4 5

24. La peur d’être

essoufflé(e)..... **0 1 2 3**

.....4 5